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Tuberculous meningitis in children

A review of 167 untreated and 74 treated patients with special reference to early diagnosis

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TUBERCULOUS meningitis occurs less often than formerly but it remains the most serious complication and the most common cause of death in tuberculous children. Clinicians agree that with current therapy a large percentage of children may be expected to recover.[1, 2] Indeed it is difficult for many young physicians to understand the helpless despair caused by this diagnosis only 20 years ago. There is general agreement that the best prognosis both for life and for complete recovery is obtained when tuberculous meningitis is diagnosed in an early stage and treated promptly.[3, 4]

Since many children are still being admitted to hospitals with far-advanced meningitis it has seemed worth while to emphasize once more the facts in the history and examination of children with tuberculous meningitis which might be of help to a physician in establishing an early diagnosis; to this end the records of 241 patients seen in the Chest Clinic of the Children's Medical

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Service of Bellevue Hospital have been reviewed. Of these, 167 children were seen before specific treatment was available and have been previously reported upon[5]; 74 were treated by antimicrobial therapy between January, 1947, and June, 1956.

The second object of this investigation was to determine, if possible, what observations might be of help in estimating the ultimate prognosis of the child receiving antimicrobial therapy; for this purpose the course of the 50 survivors of the 74 children who were treated has been analyzed. Finally, the present physical and mental state of the 50 children surviving in 1960, 4 to 13 years after tuberculous meningitis, will be reported briefly.

COMPOSITION OF THE GROUP

All children with acute tuberculous meningitis who received treatment have been included even if they survived only long enough to receive one dose of antimicrobial therapy. Streptomycin was given by the intramuscular and intrathecal routes to the first 49 patients; 25 children received isoniazid in addition and only a few of these received streptomycin intrathecally. All the treated patients were given Promizole orally for 2 to 3 years. The group studied prior to the availability of chemotherapy consisted of 167 unselected patients.

The background factors of the 167 patients in the untreated group and the 74 patients treated by antimicrobial therapy show very few differences. The age and sex composition of the two groups is similar (Table I); more than 60 per cent of the patients in each group were under 3 years of age. In the total group of 241 patients meningitis was diagnosed under 6 months of age only 4 times. The youngest patient was 4 months of age.

The seasonal distribution is strikingly similar in both groups, being highest in the spring and lowest in the autumn (Fig. 1).

Table I. Age and sex incidence of tuberculous meningitis in 167 untreated and 74 treated patients

	Untreated (167)		*Treated (74)*	
	No.	*%*	*No.*	*%*
Age in years				
Less than 1	31	18.6	13	17.5
1-2	72	43.1	34	45.9
3-4	29	17.4	11	14.9
5-9	24	14.4	12	16.2
10 and over	11	6.6	4	5.4
Sex				
Male	85		37	
Female	82		37	

Table II. Tuberculin tests at time of meningitis

	Untreated (114)		*Treated (48)*	
	No.	*%*	*No.*	*%*
Positive	94	82.5	47	97.9
Negative	15	13.2	1	2.1
Not read	5	4.4	0	0
Dosage of positive reactions:				
1 TU*	60	63.8	34	72.3
5 TU	22	23.4	0	0
10 TU	10	10.6	10	21.3
100 TU	2	2.3	3	6.4

*Tuberculin unit.

TUBERCULIN TESTS

Tuberculin tests were not repeated when there was a reliable history of a previous positive test and roentgen or other evidence of tuberculosis. Table II shows that a large percentage of the children tested at the time of diagnosis of meningitis had positive tuberculin reactions, usually with 1 to 5 T.U.* of tuberculin. All the children with negative reactions in the untreated group were tested in a late stage of meningitis, most of them only once and within a week of death. The one negative reaction found in the treated series converted to positive 4 weeks after treatment was started.

The development of better techniques and more astute detective work is reflected in the

*Tuberculin unit = 0.1 ml. of 1:10,000 dilution of O.T., or 0.1 ml. of 0.00002 dilution of P.P.D.

fact that the source case was identified in 79 per cent of the treated group compared to only 58 per cent of the first series of patients. In both groups more than half the source cases found were within the household.

The interval between the first diagnosis of tuberculosis and the onset of meningitis was known in 136 patients; symptoms developed within 3 months of a known primary tuberculosis in 41 per cent, within 6 months in 60 per cent, and within a year in 75 per cent.

The tendency of tuberculous meningitis to occur as a complication of primary tuberculosis while the disease is still in its active phase is shown also in the roentgen evidence from both groups: 75 per cent of all roentgenograms showed primary tuberculosis without calcification and an additional 14 per cent showed calcifying or calcified first infection tuberculosis.

STAGE OF MENINGITIS AT TIME OF DIAGNOSIS

At the time of diagnosis or onset of treatment 24, or 32 per cent, of the second group of patients were in the first stage of meningitis usually with no evidence of neurological involvement, 33, or 45 per cent, were in the second stage with evidence of neurological changes but no marked changes in sensorium, and 17, or 23 per cent, were in a late stage of tuberculous meningitis with marked neurological and sensorial changes. In the untreated group only 23 per cent of the cases were diagnosed early but the percentage of those first seen in a far-advanced stage was almost the same (22 per cent) as in the treated group.

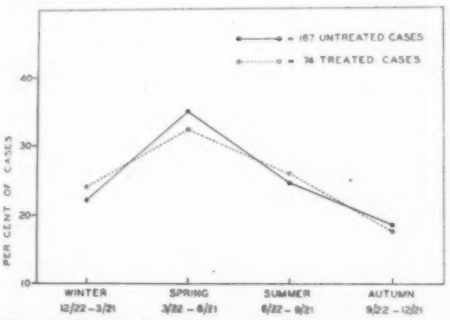

Fig. 1. Seasonal incidence of tuberculous meningitis.

POSSIBLE PRECIPITATING FACTORS

Measles was an immediate antecedent in 16, or 9.6 per cent, of the 167 untreated patients and in 9, or 12 per cent, of the 74 children who received antimicrobial therapy. The first symptoms of meningitis were most commonly noted during convalescence from measles. In 5 of the untreated patients, severe pertussis preceded meningitis but it was not mentioned as a precursor of meningitis in those who received antimicrobial therapy. Symptoms of meningitis developed within 72 hours of a severe fall or a blow on the head in 5 of the untreated and 3 of the treated patients, an incidence of over 3 per cent. In the treated group an injection of combined diphtheria-pertussis-tetanus toxoid may have precipitated the onset of meningitis in a 2-year-old boy with primary pulmonary tuberculosis. Within a few hours he developed sustained high fever, and abnormalities in the cerebrospinal fluid were first noted 7 days later when he became lethargic and vomited. A surgical procedure was an immediate antecedent of meningitis in another child who was completing a 3 months' course of streptomycin therapy for endobronchial tuberculosis when unfortunately a hypodermic needle was broken off in her thigh. She was about to be discharged 5 months later when her father demanded removal of the fragment before taking her home. This was accomplished under general anesthesia with relatively little local trauma but within 24 hours the child developed a high fever which continued without other symptoms until the sixth postoperative day when she showed the first symptoms of meningitis and the first abnormal cerebrospinal fluid.

SYMPTOMS AND SIGNS OF MENINGITIS

Usually nothing in the patient's history suggested tuberculous meningitis in the ab-

sence of knowledge that the child had a positive tuberculin test or roentgen evidence of disease. Fig. 2 has been compiled from the histories of the 241 patients who ultimately had the diagnosis of tuberculous meningitis. The three most common symptoms were fever, which was reported as a prodromal or onset symptom in almost every child, vomiting, and apathy. Upper respiratory infections not infrequently occurred simultaneously with the onset of meningitis and two thirds of these patients had acute otitis media. Headache was complained of by 20 per cent but was noted only twice in children 3 years old and never below that age; it was an early symptom in 70 per cent of children 4 years of age and older. On the other hand, a convulsion at onset, which occurred in 9.5 per cent of the entire group, was never recorded in a child over 5 years old and occurred in 17 per cent of all cases in children under 2 years of age. Abdominal pain may be a striking initial symptom. It was so definite in one patient that an appendectomy was performed which disclosed no pathologic condition in the abdomen. Constipation was reported as an early symptom in 10 per cent; diarrhea occurred only a few times.

Children first seen in later stages of meningitis presented, in addition to the early history of general symptoms, various neurological signs most of which were not specific and therefore would be of value only when the possibility of tuberculosis is remembered in differential diagnosis. More than 95 per cent of the children who presented evidence of meningeal irritation such as resistance to neck flexion, Kernig or Brudzinski signs were first examined in the second stage of meningitis or later. These signs confirmed or suggested neurological involvement but were of no help in determining its etiology. Irregular respirations with variable periods of apnea were seen in a large percentage of the cases but always associated with other signs of neurological origin.

While evidence of involvement of the cranial nerves is not pathognomonic of tuberculous meningitis it is suggestive because tuberculous exudate is most likely to be located at the base of the brain and in the basal cisterns. Findings in the 241 cases are shown in Table III. Half of the patients with involvement of cranial nerves were first seen in a late stage of tuberculous meningitis and only one patient had facial palsy without other evidence of neurological involvement. Two patients had strabismus as the first neurological sign of meningitis. Both had positive tuberculin reactions, and the diag-

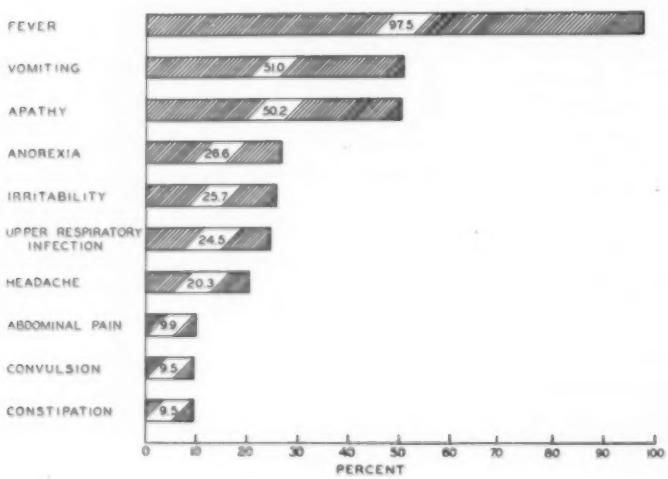

Fig. 2. Onset of symptoms in order of frequency in 241 patients.

nosis of meningitis was made by the findings in the cerebrospinal fluid.

Choroidal tubercles were found in only 21 children; miliary tuberculosis had already been diagnosed in 19 of them.

The differential diagnosis between meningitis and encephalitis presented temporary difficulty in a few untreated cases. It became much more important after treatment was available and was unusually difficult when meningitis developed during convalescence from measles. One example is cited.

T. B., a 1-year-old infant was admitted 16 days after having measles, with positive tuberculin reaction and roentgen evidence of primary tuberculosis. She was febrile and the only neurological signs were constant athetoid movements of the extremities and absence of abdominal reflexes. The cerebrospinal fluid showed a sugar content of 54 mg. per milliliter, protein of 49 mg. per milliliter, and 111 cells, 92 per cent lymphocytes. Physical examination remained unchanged but the cerebrospinal fluid 48 hours later had a sugar content which was falling but still within normal limits (41 mg. per milliliter), a marked rise in protein to 168 mg. per milliliter and 379 cells, 80 per cent lymphocytes. Treatment for tuberculous meningitis was begun at once. Subsequently, tubercle bacilli were demonstrated by cultures from the first 4 specimens of cerebrospinal fluid obtained. She never developed neurological signs characteristic of tuberculous meningitis and the sugar content of the cerebrospinal fluid never fell below normal.

In 51 of the patients who received antimicrobial therapy, the duration of symptoms before a definite diagnosis of meningitis could be measured was less than a week for 9 patients, less than 2 weeks for 21, 2 to 3 weeks for 19, and more than 3 weeks in only 2 instances. Prompt diagnosis and treatment were most critical in the fulminating cases of tuberculous meningitis which fortunately were rare.

CEREBROSPINAL FLUID

At the time of diagnosis, regardless of the stage of the disease, the majority of patients

Table III. Cranial nerve involvement; relation to stage of meningitis at time of diagnosis

	Untreated (167)		*Treated (74)*		*Total*
Facial paresis					
Stage I	1		0		1
Stage II	2		2		4
Stage III	4		5		9
Total		7		7	14
Ptosis					
Stage I	0		0		0
Stage II	3		0		3
Stage III	4		1		5
Total		7		1	8
Strabismus					
Stage I	1		1		2
Stage II	7*		6		13
Stage III	8*		3		11
Total		16		10	26
No. of patients involved	26		16		

*Bilateral in one patient.

Table IV. Average initial glucose value of cerebrospinal fluid in milligrams per milliliter in 74 treated patients

Patients in Stage I	37.4
Patients in Stage II	30.4
Patients in Stage III	27.8

Table V. Bacteriologic findings in 74 cases of tuberculous meningitis

Cerebrospinal fluid positive on direct examination, cultures negative	5
Tubercle bacilli cultured from cerebrospinal fluid	39
Tubercle bacilli found only by guinea pig inoculation	1
Diagnosis at autopsy only	5

Table VI. Relation of age of child at onset of therapy to prognosis

	No. of patients	*No. of deaths*
Less than 1 year	13	9
1-4 years	45	12
5 years and over	16	3

in both treated and untreated groups had abnormal cerebrospinal fluid conforming closely to the characteristic findings in tuberculous meningitis. All but 3 had increased cells, the sugar content was below normal (40 mg. per milliliter) in 88 per cent, and the protein content was above 50 mg. per milliliter in 72 per cent of the patients. Initial glucose values in the cerebrospinal fluid in patients with miliary tuberculosis under treatment with streptomycin were higher than in those without evidence of miliary tuberculosis. Serial examinations of the cerebrospinal fluid were of great importance in differential diagnosis. The sugar values usually fell as the protein content rose but the pleocytosis tended to remain moderate except in the rare fulminating case; the tendency to a preponderance of lymphocytes increased with successive examinations of cerebrospinal fluid. In the treated cases the average sugar content of the cerebrospinal fluid was highest in those diagnosed in the first stage of meningitis as shown in Table IV.

Bacteriology of cerebrospinal fluid. In the 167 untreated patients, all of whom died, confirmation of diagnosis was obtained by autopsy in 64 and by the finding of tubercle bacilli in the cerebrospinal fluid in 45 additional patients, a total of 65 per cent proved cases. An attempt was made to culture tubercle bacilli from every specimen of cerebrospinal fluid even during antimicrobial therapy. As shown in Table V, tubercle bacilli were identified in the cerebrospinal fluid in only 45 of the 74 patients. Proof of tuberculous meningitis was made by pathologic examination in 5 other patients. Thus 68 per cent of the treated cases were proved.

Table VII. Relation of stage of disease at onset of treatment to prognosis

	No. of patients	*No. of deaths*
First stage	24	4
Second stage	33	6
Third stage	17	14

Evidence in favor of tuberculous meningitis in the other 24 patients consisted of a positive tuberculin reaction and clinical evidence suggestive of tuberculous meningitis in all of them. In 11 instances tubercle bacilli were cultured from sources other than the cerebrospinal fluid and concurrent generalized miliary tuberculosis was present in 7 children. The initial cerebrospinal fluid findings were typical of tuberculous meningitis in all but 2 cases. Sudden high fever was the only reason for suspecting meningitis in each of these children who had primary pulmonary tuberculosis and positive cultures from gastric lavage. The protein and cell count of the initial cerebrospinal fluid were elevated, but the sugar content was normal. Treatment was initiated at once and in both cases the next examination of cerebrospinal fluid showed a sugar content below normal.

Sometimes only the initial culture, one taken before therapy or in the first few days of treatment, was positive. In about one third of the patients treated with streptomycin who had positive cultures, tubercle bacilli were present in 3 to 8 specimens of cerebrospinal fluid. Most of these were from cerebrospinal fluid removed during the first 2 weeks of meningitis. In only one patient treated with isoniazid were tubercle bacilli cultured repeatedly from the cerebrospinal fluid.

Cultures of the cerebrospinal fluid showing bacterial resistance to streptomycin were obtained in the terminal stage of meningitis from 3 patients, the last in 1950. All had shown drug susceptibility on initial cultures.

RELATION OF INITIAL FINDINGS TO PROGNOSIS

It was apparent early in the treatment program at Bellevue Hospital[6] that the age of the child at the onset of meningitis and the stage in which the disease was first treated were closely related to the outcome as shown in Tables VI and VII.

Although other investigators[7] have reported that the combination of acute generalized miliary tuberculosis and meningitis indicated a poor prognosis, this correlation

Table VIII. Relation of miliary tuberculosis to survival in 74 patients with tuberculous meningitis

	No. of patients	*No. of deaths*	*%*
Meningitis only	57	17	30
Meningitis and miliary	17	5	29

could not be shown in the Bellevue Hospital series, as shown in Table VIII. In 2 instances roentgen evidence of miliary tuberculosis had entirely disappeared before meningitis developed. One of these patients survived and one died.

COURSE OF MENINGITIS IN RELATION TO PROGNOSIS

Course of cerebrospinal fluid. The changes in the cerebrospinal fluid content of protein and sugar have been studied in all patients who survived 3 months. The sugar tended to return to normal much earlier than the protein. The most rapid return to persistently normal sugar content was in 19 days, the slowest 11 weeks. The rate of return to normal was unrelated to the amount of sugar found on the diagnostic taps or to the development of sequelae of the meningitis.

Electrolyte disturbances. Respiratory acidosis of metabolic origin was diagnosed in 4 children, none of whom survived; renal tubular calcification was found on postmortem examination in 2 other cases. The diagnosis of electrolyte disturbance was made in only one patient who survived; she had hyponatremia, hyperchloremia, a low carbon dioxide, abnormally high blood urea, elevated blood pressure, and generalized calcinosis which eventually disappeared. However, complete blood chemical studies were not always obtained.

Secondary pyogenic meningitis. Secondary infection occurred 6 times. Two patients with far-advanced meningitis were receiving steroids in addition to antituberculosis drugs and other antibiotics; in one patient the septic meningitis was thought to be secondary to phlebitis following a cut-down procedure, and in the other a leaking burr hole may have been the portal of entry. Both patients died. Another patient developed fatal meningitis due to *Staphylococcus aureus* after a shunt operation for hydrocephalus following arrest of tuberculous meningitis.

Three patients developed meningitis due to *Streptococcus faecalis* following infection from a contaminated vial of streptomycin. Although the infection was apparently controlled in 2 of the children, all 3 died, and the secondary meningitis probably contributed to their deaths.

Marked neurological abnormalities during course of meningitis. These were seen much more frequently in patients who died than in those who survived. In the 50 children who survived, decerebrate rigidity and spastic quadriplegia occurred twice, persisting in one infant in whom meningitis was first diagnosed late in the third stage and clearing completely in another patient whose diagnosis was made and treatment begun in an earlier stage of the disease. Eleven survivors had hemiplegia during the course of the meningitis which cleared completely in 4 instances. One patient with no changes in the eye grounds was apparently completely blind for a month and recovered with normal vision. Convulsions developed in the course of meningitis in 10 children who survived. The seizures seemed to be due to streptomycin administered by the intrathecal route in 5 of them; they had no subsequent convulsions. The remaining 5 children had their first seizures one to 3 months after the onset of meningitis; 3 of these developed epilepsy.

Electroencephalograms. Most of the tracings in children who died were markedly and diffusely abnormal and some had local-

Table IX. Electroencephalograms in 48 survivors

Always normal	14
Abnormal to normal	22
Always abnormal	8
Normal to abnormal	4

izing abnormalities as well. All but 2 of the 50 who survived meningitis were tested and their electroencephalograms are classified in Table IX. Only 4 of those who were always normal had initial tracings made within 3 months of the onset of meningitis. Reversion from abnormal to normal was observed as long as 4 years after meningitis. Of the 8 children with persistently abnormal tracings, 5 later developed convulsions; another continues to have spastic quadriplegia and one is mentally defective. However, one older girl has never shown any abnormality and is doing well in high school. Normal electroencephalograms became abnormal as long as 26 months later; 2 of the 4 eventually reverted to normal but abnormalities have persisted for more than 5 years in 2 patients, one mentally deficient and one epileptic.

Subarachnoid block and arachnoidal adhesions. Clinical evidence of damage attributable to repeated spinal punctures was constantly sought. The 50 survivors all had repeated taps and streptomycin was administered by the intrathecal route in 39. Three showed symptoms or signs which might be attributed to spinal arachnoiditis.

Case 1. Six days after onset of the original attack of meningitis in a 6-year-old girl weakness of the left leg was noted, associated with diminished sensation to pinprick. She developed a complete flaccid paralysis of the left leg with only slight movement in the toes; left tendon reflexes were absent and she complained that her leg was "asleep." After 6 months of therapy she still had a foot drop and pain on motion. Because of relapse of the meningitis this child had a total of 137 lumbar punctures and 107 intrathecal injections. Ten years later she still lacks pain and temperature perception up to the left knee, the knee jerk is diminished, and ankle jerk is absent; there is loss of position sense in the left toes with inability to dorsiflex. She wears a half-size smaller shoe on the left foot than on the right.

Case 2. A 13-year-old girl complained bitterly of pain radiating down her right leg following lumbar punctures; the period of greatest intensity apparently occurred about 6 weeks after the beginning of treatment. Two months after admission atrophy of the right calf and foot drop were noted. This girl had a total of 124 punctures with 90 intrathecal injections. Five and a half years later she still has slight weakness in dorsiflexion of the right foot and her right calf is smaller than the left. During parturition recently she had normal labor pains but had no pain associated with delivery.

Case 3. A girl 18 months of age was deaf after treatment with streptomycin for meningitis but apparently had no other residua. She had received 66 intrathecal injections and a total of 121 spinal taps. After 6 months of streptomycin by the intramuscular route the protein content of the cerebrospinal fluid was normal and remained so. Five years later, after a fall, she complained of pain in the right hip and dragged her left leg. She showed limitation of back motility and some tenderness over the lumbar spine and right sciatic notch; there was no motor palsy and plantar reflexes were normal. She refused to walk and complained of pains on trying to stand. The cerebrospinal fluid showed a protein content of 160 mg. per cubic centimeter, but cells and sugar content were normal. One month later she exhibited limitation of extension at both knees, more on the left, probably associated with contractures. Knee and ankle jerks were absent and some atrophy was present in the anterior tibial group of muscles. The symptoms gradually subsided but reflexes remained absent. A myelogram showed a filling defect between L-2 and L-3. Lami-

Table X. Relation of findings on pneumoencephalography to stage of meningitis at onset of therapy in 29 patients

Findings on pneumoencephalograms	*Stage of meningitis*		
	I	*II*	*III*
Normal	12	4	0
No filling of ventricle	0	0	1
Hydrocephalus			
Slight	1	0	0
Moderate	0	4	2
Severe	1	1	3

nectomy was performed and a fibrofatty tissue mass was found involving the cauda equina roots and the adjacent subdural and epidural spaces. It was decided not to attempt to dissect the mass from the underlying nervous elements because of the danger of destroying healthy nerve roots. At the present time, 9 years after the meningitis and 3 years after operation, she still has a slight limp but no atrophy; reflexes are normal. She skates and dances and behaves like a normal child.

Eighteen of the 74 treated children had evidence of obstruction of the spinal fluid space. This was demonstrated in 12 of the 24 fatal cases and in only 6 of the survivors. Most of the blocks were found in children who had received streptomycin by the intrathecal route; in one instance, however, obstruction was diagnosed before therapy was begun. Two patients received no streptomycin intrathecally but were admitted in a very late stage of tuberculous meningitis. The spinal fluid was frequently xanthochromic with protein values greater than 300 mg. per cent; pressures were low with absence of the normal rise on jugular compression. There was frequent spontaneous jelling of the fluid.

When the obstruction of spinal subarachnoid space extended into the basilar cisterns it produced the apparent paradoxical situation of a low spinal fluid pressure and progressive hydrocephalus. In those who survived meningitis it was demonstrated 3 times by ventriculography. In an additional 2 patients in whom the spinal block was incomplete it was possible to show evidence of hydrocephalus by pneumoencephalography.

When only obstruction of the basal cisterns was present, hydrocephalus evidenced by progressive increase in the pressure of the cerebrospinal fluid was demonstrated by pneumoencephalography in 8 children.

Aside from antimicrobial agents various additional methods of therapy aimed at dissolution of the block were tried. Tuberculin,[8] streptodornase and streptokinase[9] and pancreatic dornase[10] were given by the intrathecal route. Evidence of resolution of the obstruction was obtained in one patient by the use of pancreatic dornase. Air studies of this patient have been published previously.[11] Although 11 children with block survived, only 3 have no sequelae.

Pneumoencephalograms. Pneumoencephalograms were made on 29 of the 74 patients. Abnormalities were found in 13: no filling of the ventricles with a basal block in one instance and definite hydrocephalus in the others. As shown in Table X, most of the abnormal air studies were obtained in patients in whom the diagnosis was made late and whose treatment consequently began after the development of neurological signs. Only one patient with severe hydrocephalus survives but in a decerebrate state. Of 6 patients with moderate hydrocephalus, 2 are dead, 2 have marked evidence of organic brain disease, and 2 are at home leading essentially normal lives.

Unilateral cerebral atrophy was also demonstrated by air studies in 2 patients, both with mild residual hemiparesis.

Relapse. Relapse is defined as renewed clinical or laboratory evidence of tuberculous meningitis after a period during which the patient has been free from symptoms and signs of meningitis and the cerebrospinal fluid has been within normal limits.

During the period when streptomycin was the most effective antimicrobial agent, the number of patients initially reported as survivors of tuberculous meningitis frequently diminished as relapses occurred. This was particularly true of reports of adult patients. The Committee on Medical Research and Therapy of the American Trudeau Society[12] commented in 1951 on the high incidence of fatal relapse "even when an early remission is attained." It is probable that many patients relapsed because of insufficient therapy. Yet it is doubtful whether better methods of therapy have entirely eliminated the risk of relapse. It seemed wise therefore to examine the information about relapse in the Bellevue Hospital patients and review important factors in the early recognition of relapse, and to inquire whether there seem to be factors inherent in the patients or in

aspects of their disease which predisposed them to relapse.

Three relapses occurred in the 49 patients treated before the introduction of isoniazid into the therapeutic regimen. All patients during this period received streptomycin therapy by the intrathecal route for about 6 weeks and streptomycin therapy by the intramuscular route for about 6 months, combined with Promizole, after which they received only the sulfonamide for a total duration of 3 years. The general condition of the 3 patients under consideration was good at the end of streptomycin therapy; neurological signs were absent and the cerebrospinal fluid was within normal limits. Repeated cultures of the cerebrospinal fluid had been negative. The patterns of relapse were strikingly similar. Within 15 to 43 days after streptomycin was stopped a fall in the sugar content of the cerebrospinal fluid and a rise in protein content with an increase in cells were noted on routine re-examinations of the cerebrospinal fluid. There was a striking absence of physical signs or other symptoms of illness except for a rise in temperature. The characteristic picture of the cerebrospinal fluid is best seen in graph form in Fig. 3. In the 3 patients tubercle bacilli were recovered by culture soon after the time when the lines of rising protein and falling sugar content crossed. The organisms were susceptible to streptomycin. Although no relapses have occurred since isoniazid has been added as an antimicrobial agent, it seems wise to bear the possibility of relapse in mind and to examine the cerebrospinal fluid when a child convalescing from tuberculous meningitis has an unexplained rise in temperature.

Although only 15 of the 47 patients treated with streptomycin and Promizole were white, the 3 children who relapsed were white. Moreover only 11 of the 47 had roentgen evidence of calcification in the primary focus, but 2 of the 3 children who relapsed had well-calcified lesions. This may suggest that a well-established cortical or meningeal metastasis may not be as susceptible to complete cure by antimicrobial therapy as a more recent seeding.

Analysis of deaths. Of the 74 patients, 2 died, 22 while still under treatment, 2 after the meningitis was arrested. One child died within 24 hours of admission, 14 in the first 3 months of treatment, 4 in 6 months to one year, 2 in the second year, and 3 more than 2 years after the onset of the meningitis.

Two of the late deaths were due indirectly to hydrocephalus. In one boy 2 years after recovery from meningitis, an excessive amount of air was introduced in an injudicious attempt to prove hydrocephalus in a child in whom previous attempts at a pneumoencephalogram had been unsuccessful; another child with arrested meningitis but residual severe hydrocephalus died of septic meningitis following an attempted shunt. One child died 2 years after meningitis of "bronchopneumonia" in an institution for mentally retarded children. Eighteen of the 24 deaths occurred before isoniazid was added to the therapeutic regimen. Included in the 6 deaths of those treated with iso-

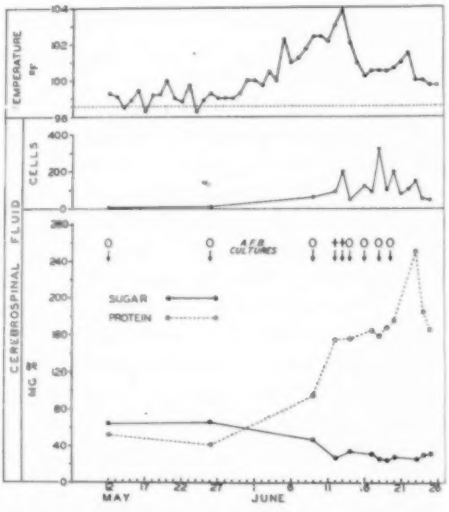

Fig. 3. CSF changes, temperature, and results of cultures of CSF during relapse from meningitis. SM discontinued April 30, CSF and temperature within normal limits through May 27. Gradual rise of temperature, increase in cells and protein with fall of sugar content of CSF. On June 12 sugar below normal and culture positive for tubercle bacilli.

niazid are those of the child who died 2 years later of bronchopneumonia and of the child who died within 24 hours of admission; the 4 others were all admitted in a late stage of meningitis.

Neurological sequelae in survivors. Neurological sequelae are present in 12, or 24 per cent, of the 50 survivors. One child admitted with spastic quadriplegia is still living, her acute meningitis arrested but her condition unchanged more than 6 years after the onset of meningitis. This patient was treated with isoniazid but steroid therapy was not yet in use at the time of her illness. Seven patients have hemiparesis, so minimal in 2 as to be hardly noticeable and severe in only one child who also had tuberculosis of the hip. One boy has gross ataxia so severe that he falls frequently. The remaining children with neurological sequelae are the 3 with residuals of arachnoiditis who have been previously described.

Eighth nerve function.

Hearing. Serial audiograms were made on 45 of the 50 survivors. Two children with chronic otitis media had conductive loss. Seventeen patients had severe perceptive loss and 7 others had loss to high tones only. All had received streptomycin by the intrathecal as well as by the intramuscular route. Survivors who received no intrathecal therapy with streptomycin had no perceptive loss of hearing.

Vestibular function. This was assessed in 48 of the 50 survivors with the use of the cold caloric test and, when the children were out of bed, the rotation method. Repeated tests were made in the majority. Only 7 children have completely normal vestibular function; of these, 5 received intrathecal streptomycin. Thirty-eight of the 48 have absent function which appeared to be permanent in that it has persisted throughout the period of follow-up. One of these had unilateral loss, though function was hypoactive in the other ear. The remaining 3 children have hypoactive function bilaterally; 2 received no intrathecal streptomycin.

Many children were ataxic during and at the end of intrathecal therapy, but compensated quickly, and, with one exception, now show no subjective evidence of vestibular impairment. Direct questioning of some of the older children has not revealed any unsteadiness in the dark. One child remains grossly ataxic, but absent vestibular function alone seems most unlikely to be the cause of his disability.

Intracranial calcification. This has appeared so far in 21 of the 50 survivors. In 20 instances it was first observed 2 to 8 years after onset of meningitis; in one patient with idiopathic hypercalcemia a cluster of small calcifications was seen on the first skull roentgenogram. The many other areas of calcification disappeared within a few months but the intracranial calcification has remained unchanged for 7 years. In 18 patients the calcification appeared to be in the region of the basal cisterns, interpeduncularis, chiasmatis, and ambiens; the calcification seemed to be in the brain substance in only 3 instances. Usually the calcification appeared to become denser during the first year after its initial appearance and then remained stable. In no case has it, as yet, disappeared or become less obvious on repeated examinations. Only 5 of the patients who show intracranial calcification received specific therapy in the first stage of meningitis.

Obesity. Five of the 50 survivors (4 males and 1 female) are 60 per cent or more over average weight and have abnormally large appetites. However, at least one of them was obese and had polydipsia and polyuria before he contracted meningitis.

Psychometric evaluation. Adequate and usually repeated testings have been done on 47 of the 50 survivors. The remaining 3 patients are assessed by their physicians, family, and teachers as of at least average intelligence. Seven children, including 4 who have severe perceptive hearing loss, have been classified as bright to superior (I.Q. 110-130). Seventeen children are assessed as average (I.Q. 90-110). To these should probably be added the 3 children who have not been formally tested. Intelligence quotients of 80-90 interpreted as dull normal have been found in 5 survivors, and an additional 8 fall

into a borderline group with I.Q.'s of 70-80. Thus 40 of the 50 survivors have a distribution of intelligence ratings which is similar to that seen in the general pediatric outpatient department of Bellevue Hospital. Thirty-eight of these survivors are working or attending school in the proper grades for their ages; the remaining 2, one of average and one of borderline intelligence, are in institutions for epileptics. Nine children are mentally defective. These include one child with persisting decerebrate rigidity and one with hemiplegia who are imbeciles, as well as a third hemiplegic child originally considered dull who after repeated convulsions now has an I.Q. of 29. The remaining 6 mentally deficient children have I.Q.'s between 50 and 70.

At least 4 survivors, 2 of them with high I.Q.'s, have had evidence of organic brain damage, aside from epilepsy, such as severe temper tantrums and hyperkinesia. All these children are deaf and it is hard to separate the emotional difficulties due to lack of hearing from those due to cerebral involvement. In all but one case, there has been a great improvement with time, with the children eventually making good adjustments.

In all, 23 of the 50 survivors are handicapped either by severe hearing loss, other neurological abnormalities, brain damage or intelligence quotient below the borderline level, or by combinations of these difficulties. Children treated while still in the first stage of meningitis have the least number of handicaps as do those who were treated with isoniazid and with streptomycin by the intramuscular route. Despite their handicaps 40 of the 50 survivors are living otherwise normal lives, are attending school or working, and making good adjustments.

DISCUSSION

Early diagnosis of tuberculous meningitis could not alter the outcome before antimicrobial therapy was available but it became a deciding factor in obtaining a good prognosis in the group of cases treated by specific therapy. It is the most important point to stress in any discussion of the prognosis of tuberculous meningitis in children. Miraculous as results seem in contrast to those of fifteen years ago, the best results still depend to a large extent on prompt recognition and treatment. As tuberculous meningitis becomes less and less common as a result of public health measures and of prophylactic therapy of primary infections,[13] it is more important than ever to remember tuberculosis in the differential diagnosis of fever of unknown origin. In this series of 241 patients meningitis was diagnosed throughout the pediatric age range; the index of suspicion should be highest in children 1 to 2 years old.

While the seasonal incidence was highest in the spring, and this is true in other reported series, meningitis does occur in every month of the year and the seasonal incidence is not of help in an individual case.

A tuberculin test should never be omitted once suspicion has been aroused; it was not often negative in patients with tuberculous meningitis and then usually in those in advanced stages. In the treated group only one child was initially negative to tuberculin. The absence of a positive tuberculin test, while it does not absolutely exclude tuberculosis, weighs heavily against this diagnosis. A history of recent conversion of the tuberculin test to positive is important because in this series, as in others,[14] meningitis tends to be an early complication of primary tuberculous infection.

A history of contact with a case of tuberculosis should always be sought in a suspected case. This was obtained in a high proportion of this series. A history of measles preceding the illness should heighten the suspicion of tuberculosis. Pertussis was not mentioned as an immediate antecedent in the group who received specific therapy, probably reflecting the marked decline in the frequency and severity of pertussis in the New York area. Other possible precipitating factors should be noted, such as severe reaction to immunizations, head injuries, or recent surgical procedures.

A roentgenogram of the chest should always be obtained when the tuberculin reac-

tion is positive and, when suspicion of tuberculosis remains, even in the absence of a positive reaction. For over thirty years close to 90 per cent of all children with tuberculous meningitis seen at Bellevue Hospital have shown evidence of primary pulmonary tuberculosis.

The most constant complaints were fever (in all but 6 patients) and vomiting and apathy, which were noted in half of the children. These symptoms are common to many diseases of children but are of great importance when an additional history of a combination of irritability with periods of lethargy is obtained.

Many patients in the first stage of meningitis have infections of the upper respiratory tract. This fact should be remembered when the concurrent fever and irritability or lethargy seem out of proportion to the obvious infection or when general symptoms persist after improvement in the local manifestations. Catarrhal and occasionally purulent otitis media were seen in 16 per cent of the patients. Abdominal pain without local evidence of involvement is a more uncommon early symptom but striking when it occurs and was seen only in the oldest age group.

When the patient is first seen in the second or third stage of meningitis the diagnosis of intracranial disease is usually obvious, but the cause must still be determined. Knowledge of the presence of primary tuberculosis in the child should lead to strong suspicion of tuberculous meningitis.

Differentiation of the cause of neurological signs in patients in the second and third stage of tuberculous meningitis may be assisted in some cases by the finding of choroidal tubercles. In the Bellevue series, however, these were found in only 2 patients in the absence of roentgen evidence of miliary tuberculosis. Purulent meningitis is usually easy to exclude except in the occasional patient who has been inadequately treated or in a chronic *Hemophilus influenzae* infection, especially in the event of a walled-off cerebral abscess. The use of a combination of streptomycin and penicillin for suspected meningitis of unknown origin should be discouraged because the streptomycin may mask symptoms and delay the diagnosis of tuberculous meningitis. Glucose by the intravenous route should be avoided since information about the sugar content of the cerebrospinal fluid may be important in differential diagnosis. Careful study of the cerebrospinal fluid will usually rule out uncommon infections such as torulosis. Rarely malignancy will simulate the clinical and cerebrospinal fluid findings of established tuberculous meningitis.[15] Tuberculous meningitis with early neurological signs may easily be confounded with viral infections of the central nervous system, especially when the symptoms of encephalitis, which are present to some extent in all tuberculous meningitis, happen to predominate over those due to involvement of the meninges. The differential diagnosis can be made by watchful waiting since the protein content of the cerebrospinal fluid rarely remains high for long in viral infections and tends to rise steadily in untreated tuberculous meningitis and the sugar content of the cerebrospinal fluid tends to fall and reach lower levels than in viral infections. Since the prognosis of tuberculous meningitis depends in part on the stage in which it is treated, however, waiting is a dangerous method of diagnosis. One should always bear in mind that tuberculous meningitis is a complication susceptible of complete cure if treated early and vigorously, whereas no specific therapy exists for many of the diseases which are commonly considered in differential diagnosis. Therefore isoniazid treatment should never be withheld because a definite diagnosis of tuberculosis cannot be made. One cannot afford to wait for the demonstration of tubercle bacilli in the cerebrospinal fluid. Moreover, they cannot always be demonstrated either by direct examination or by culture in undoubted cases of tuberculous meningitis. The decision in many published series to omit cases in which tubercle bacilli could not be demonstrated in the cerebrospinal fluid especially in single examination undoubtedly leads to omission of cases of tuberculous meningitis. In the series reported from Bellevue Hos-

pital careful search and repeated cultures failed to demonstrate tubercle bacilli in 3 patients in whom a pathologic diagnosis confirmed the cause of death as tuberculous meningitis.

Regardless of the stage of meningitis in which the patient is first seen the diagnosis is usually confirmed by examination of the cerebrospinal fluid. Sometimes the results are typical even before neurological symptoms have developed. Only 3 patients in this entire series had less than 10 cells, and in each case the chemical data were markedly abnormal, the sugar in one case being 17 mg. per milliliter with only 6 cells. In the treated series the patients with miliary tuberculosis under treatment with streptomycin often had a sugar content of the cerebrospinal fluid within normal range during the early phase of meningitis. No explanation of this phenomenon is available. Only 4 other children of the 241 had normal sugar values in the cerebrospinal fluid at the time of diagnosis. A few children had normal protein values with low sugar content and an increased number of cells. No patient had a completely normal cerebrospinal fluid at the time of diagnosis. Serial examinations were of great value since the sugar content of the cerebrospinal fluid usually diminished progressively on successive examinations even before it became abnormally low.

In the Bellevue Hospital series the outcome of patients with tuberculous meningitis could be correlated with the stage in which treatment was initiated and with the age of the patient. Older children had a better prognosis than infants, both as regards survival and the physical and mental status of the survivors. Patients treated in an early stage of meningitis also fared better than those whose disease was discovered in an advanced state. Contrary to the finding of some other investigators the prognosis in the Bellevue Hospital series did not vary with the presence or absence of roentgen evidence of miliary tuberculosis. The sugar content of the cerebrospinal fluid on initial examinations also furnished some indirect leads to prognosis since it was found that the glucose value of the cerebrospinal fluid was highes in patients in Stage I and lowest in Stage III

The large number of lumbar puncture considered necessary in the treatment o meningitis stirred apprehension regardin local damage. But in view of the prognosi of untreated meningitis no one wanted t limit the number of examinations of th cerebrospinal fluid which seemed necessary for control and proper supervision. Before the use of isoniazid, intrathecal therapy with streptomycin was deemed necessary. Diagnostic studies were performed on fluid withdrawn at the time of administration of the streptomycin. Findings suggestive of obstruction of the spinal subarachnoid space could be verified by the streptomycin diffusion test[16] or the sugar diffusion test[17] but neither test localized the site of the obstruction. With the use of isoniazid, streptomycin therapy by the intrathecal route was discontinued and the number of lumbar punctures was diminished. The need for repeated examinations of the cerebrospinal fluid to evaluate the course and the effectiveness of therapy was not obviated, however.

Information about possible damage to the spinal cord by repeated lumbar punctures was sought in the postmortem findings of 9 children in whom complete examinations of the spinal cord were made. These children died after prolonged therapy with streptomycin by the intrathecal route and had therefore been subjected to a maximal possibility of trauma. Epidural hemorrhage in the lumbar region was found in 4 instances; 2 of these had no significant involvement of the spinal subarachnoid space and 2 had incomplete obstruction due to diffuse inflammatory processes. Localized exudate in both the midthoracic and lower lumbar regions was found in a fifth case but the area between was smooth and glistening. Extensive obstruction of the spinal subarachnoid space by inflammatory process was found in 2 other cases. In neither, however, was there any significant change at the site of lumbar punctures; in one of these cases there was a hemorrhage in the thoracic area. In the remaining 2 cases no changes were found in

the spinal subarachnoid space. Thus, in these 9 cases, only 2 had any significant subarachnoid involvement at the lumbar puncture sites and 3 had extensive changes distant from the puncture sites.

The presence of fibrofibrinous adhesion about the spinal cord proper has not proved to be of any serious neurological significance in the survivors of tuberculous meningitis. In 3 cases the conus-cauda equina area was involved and neurological symptoms were produced. It is probable that this area was involved in other patients without focal neurological manifestations since the site of obstruction was not always determined. The 3 patients have neurological residuals, although in 2 they are minimal. In one of the latter 2, myelography, and after much discussion, laminectomy, were performed. In part, the operative procedure was stimulated by a report[18] of a series of cholesteatomas found in the intraspinal space in children previously treated for tuberculous meningitis. It is our present impression that the reported cholesteatomas were a result of the local techniques utilized.

It is our opinion that multiple, properly performed, lumbar punctures do not adversely affect the prognosis and do give valuable information that will guide the physician in his handling of each case. It is only through lumbar punctures that one can determine whether or not the cerebrospinal fluid is returning to normal and whether or not an obstruction of the spinal fluid pathways is developing. Lumbar puncture will provide the clue as to when special studies such as pneumoencephalography are indicated.

In studies of the untreated group of patients it was noted[5] that children who died within 3 weeks after the onset of the disease rarely showed evidence of hydrocephalus. This is understandable when it is recalled that the condition is a diffuse one, best classified as a meningoencephalitis. As the disease progresses, vascular changes occur and may result in varying degrees of cerebral atrophy. Fibrin is deposited and gradually replaced by fibrous tissue. A critical area in the cerebrospinal fluid pathway is that of the basilar cisterns at the tentorial aperture. Fine tissue septae traverse the spaces and they are readily occluded by fibrin deposits. Clinically the situation is manifested by increasing irritability and lethargy. Spinal fluid studies show increased pressure and the obstruction can be demonstrated by air studies. Varying degrees of hydrocephalus develop. Spontaneous arrest of the hydrocephalus may occur; the reason for this is not clear. Theoretically, it should be possible to reverse the obstruction in the fibrinous stage. However, in spite of the use of enzymes and tuberculin intrathecally and corticosteroids intramuscularly and intravenously, in 2 cases, in addition to antimicrobial therapy, there was failure to reverse basilar obstruction. In one case, a less frequent obstruction occurred at the foramina of exit from the fourth ventricle and release of the obstruction followed the use of pancreatic dornase.

The clinical course and results of special examinations of each survivor were scrutinized in order to determine retrospectively which might have helped in predicting the prognosis of the individual patient.

About 20 per cent of the survivors had symptoms and signs early in the course of their meningitis which emphasized involvement of the cerebrum; sometimes there were no symptoms of meningeal involvement. In some these symptoms disappeared during the first weeks of illness and these children have no evidence of brain damage, whereas those in whom symptoms of extreme restlessness or weakness, athetoid movements, marked tremor, slurred speech, grimacing, chewing, disturbances of vision, and other signs of encephalitis persisted for weeks or months have shown evidence of brain damage in behavior difficulties, late development of convulsions, or late mental deterioration.

Convulsions occurred at some time in 20 per cent of the patients who survived. Those associated with drug administration had no sequelae. Of the 8 children who had convulsions at onset only 2 had later seizures after apparent recovery from the meningitis. Three of the 5 who had their first convul-

sions (not associated with antimicrobial therapy) later in the course of meningitis developed epilepsy. All of the 5 patients who had seizures after discharge and apparent recovery from tuberculous meningitis had had previous convulsions. Four of them had persistent abnormal electroencephalograms; in one the EEG remained normal for 2 years and since then has been abnormal. The occurrence of one or more convulsions therefore seems to increase the likelihood of permanent damage, especially if the EEG remains abnormal. One infant who had only one convulsion at the very onset of her meningitis but whose EEG's continued abnormal had no further seizures until three years later when she developed severe epilepsy.

Persistently abnormal EEG's during the course of meningitis and later apparently generally indicate a poor prognosis, even in the survivors who have not had convulsions. Of the 8 children who have never had a normal reading only one older girl is not handicapped in any way and is doing well in high school. There were only 2 instances in which after a normal EEG had been recorded later persistent abnormal records were obtained. Whenever possible prognosis should be predicated only on a series of electroencephalograms.

In general, a normal pneumoencephalogram early in the course of meningitis was related to a good prognosis. Obstruction at the basilar cisterns indicated a poor prognosis with progressive hydrocephalus or, at best, spontaneous arrest of the hydrocephalus.

The development of calcifications in roentgenograms of the skulls of survivors of tuberculous meningitis has been discussed by Lorber[19] and others. Calcifications have appeared to date in almost half of the survivors of the treated Bellevue Hospital series. The area of calcification is in general much smaller than in Lorber's cases and in only 3 instances was a minute calcification seen in the brain substance. The remaining calcifications were in the area of the basal cisterns and probably due to healing of caseous exudate. In this series there is certainly no relation between the presence or absence of residual calcification and prognosis.

The fallacy of relying on single psychometric evaluations in the estimation of prognosis is best illustrated by the results of serial psychometric examinations in the survivors of tuberculous meningitis. Repeatedly, an assessment of mental retardation was made because of the finding of a low intelligence quotient in a child convalescing from meningitis who later showed at least average intelligence. One child's intelligence quotient a year after onset of her illness was 67 and rose in successive examinations to 115 three years later and has remained at that level. Conversely a few have deteriorated. One infant who survived meningitis was apparently very bright but was deaf and showed evidence of brain damage by behavior difficulties. At the age of 6 his I.Q. was still in the superior range but eventually remained stabilized in the borderline area. The prognosis of mental capacity should therefore never be dogmatically determined during early convalescence but only after prolonged observation and repeated examinations.

The group of survivors who have been presented after a follow-up period of 4 to 13 years were all treated before June, 1956; none have had the benefit of steroid therapy. Two thirds of them received streptomycin by the intrathecal route and many of these have loss of auditory and vestibular function. Yet it is amazing that 40 of the 50 survivors are leading fairly normal lives and making good family and school adjustments, in many cases after long periods of observation and of rehabilitation procedures.

CONCLUSIONS

1. In 241 patients with tuberculous meningitis the dominant early symptoms were fever, vomiting, and apathy.

2. In the 74 treated cases the survival rate could be directly correlated with the stage of the disease at onset of therapy.

3. Tuberculosis should always be suspected as the cause of fever and other general symptoms beginning during convalescence from measles.

4. Symptoms of upper respiratory infection frequently obscured early tuberculous meningitis.

5. A history of contact, a positive tuberculin reaction, and roentgenographic evidence of pulmonary tuberculosis were important factors in diagnosis.

6. In the differential diagnosis of children with signs of neurological origin a chest x-ray should be obtained.

7. A tentative diagnosis can be made in practically every case by examination of the cerebrospinal fluid.

8. Treatment should not await bacteriologic confirmation.

9. Serial lumbar punctures should be performed to evaluate the course of the disease.

10. In survivors, an ultimate prognosis can be estimated only after prolonged observation and evaluation of electroencephalographic and psychometric studies.

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Transitional distress in infants of diabetic mothers

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THE clinical behavior of neonates whose umbilical cords continued to pulsate for prolonged periods after birth has been described in a recent publication.[1] Ninety-three per cent (38 of 41) of these infants had some degree of difficulty in adaption to extrauterine life. The source of distress in the minority appeared to be "intrinsic"† or within the infant himself. In the majority, however, the source of distress was felt to be extrinsic† to the infant, originating in a disturbed intrauterine environment. The symptomatology of the majority developed in an orderly sequence, and was considered to represent a recovery process as the infant overcame the depressive effects of prior asphyxia and/or the depressive effects of drugs administered to the mother. The total symptomatology was termed *transitional distress.*

Since 4 of the 41 infants with prolonged umbilical cord pulsations were infants of diabetic mothers, it became of interest to compare the symptomatology of consecutive liveborn infants of diabetic mothers with the symptomatology previously described in infants with pulsating cords. This paper includes the description of the clinical behavior of 28 infants of diabetic mothers together with a comparison of the symptomatology in the distressed infants with the symptomatology previously described as transitional distress. A discussion of the pathogenesis of early distress and a follow-up report on these patients are also presented.

SUBJECTS AND METHODS

The infants included in this study are consecutive liveborn infants of diabetic mothers delivered on the clinic services of Jefferson Davis and Hermann Hospitals over a 2 year period (23 cases), and infants seen by one of the authors in a private pediatric practice

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†*Several authors[2, 3, 4] have used the terms "intrinsic" and "extrinsic" in classifications of causes of perinatal infant morbidity and mortality. Intrinsic disease, as used in this paper, is an entity existing within the infant himself and capable of producing symptomatology after birth (anemia, infection, congenital anomalies, etc.). Extrinsic disease here refers to disturbances arising in response to adverse intrauterine influences which terminate with delivery (asphyxia, drug effect, effects of disturbed maternal physiology, etc.).*

over the same period of time (7 cases). The infants were kept under close physician surveillance during their hospital stay.

Two infants had congenital malformations (intrinsic disease). They have been excluded from this study because of possible relationships between the malformations and their symptomatology.

RESULTS

Clinical behavior of infants. The 28 infants described here had no evidences of intrinsic disease on physical examination (Table I). Seven had no difficulty with the onset of respiration at birth and no difficulties were observed during the period of hospital stay (Group A). Five had transient and variable symptoms without a definite clinical pattern (Group B). Sixteen infants had a sequence of cardiopulmonary and neurological distress (Group C).

The transient signs observed in the 5 infants of Group B varied in age at onset (birth to 48 hours) and in duration. These disturbances were: poor condition at birth (1), cyanosis (2), visible cardiac thrust (1), transient cardiac murmur (2), tachycardia (1), mild clinical jaundice (2), hyperactivity (1), and prolonged pulsations of the umbilical cord (2). In the latter cases the cord continued to pulsate for 1 hour and 10 minutes, and for 1 hour and 45 minutes, respectively.

The cardiopulmonary and neurological symptoms of the 16 infants of Group C began close to the time of birth (Table II). Abnormal findings were apparent at birth in 5 infants, and abnormalities developed during the first hour of life in 10 infants. The latest time of onset of distress in this group was 1 hour and 45 minutes following delivery. The duration of distress ranged from 4 hours to 11 days, with an average duration of 98 hours.

Table I. Grouping of infants of diabetic mothers according to symptoms observed (infants with intrinsic disease excluded)

Group A	No observed distress	7 cases
Group B	Transient symptomatology without definite clinical pattern	5 cases
Group C	Transitional distress (cardiopulmonary and neurological distress)	16 cases

Although the clinical manifestations shown by infants of Group C (Table II) were both cardiopulmonary and neurological, they were of equal prominence in only 8 of the 16. In the remaining 8 infants, cardiopulmonary symptoms dominated in 3, and neurological symptoms dominated in 5. The signs and symptoms of both cardiopulmonary and neurological distress developed in an orderly sequence of 3 phases (Table III). The direction of symptomatology altered as the infant appeared to improve or to deteriorate clinically. With clinical improvement, the symptomatology progressed from that of Phase 3 to Phase 2 to Phase 1. With clinical deterioration, the order was reversed (Phase 1 to 2 to 3).

The symptoms of the 16 patients of Group C developed in phases as described below. (The cardiopulmonary and neurological symptoms are also outlined in Table III; the rationale for the numbering and order of the phases is discussed in the legend.)

Phase 3.

Cardiopulmonary. In the portion of Phase 3 corresponding to the deepest depression, respiration was gasping and slow. With improvement, respiration became labored with grunting and finally progressed to a more rapid rate with or without retractions. At the same time the heart rate changed from a bradycardia to a normal rate with loud, clear sounds. The second pulmonic sound was often accentuated.

Neurological. Throughout Phase 3, the infant's activity was diminished to absent. The reflexes (Moro, suck, withdrawal, grasp, etc.) were diminished, and the muscle tone was poor. Parasympathetic effects predominated.

Phase 2.

Cardiopulmonary. With the onset of Phase 2, the respiratory rate continued to increase and respirations became shallow with inter-

Table II. Transitional distress in infants of diabetic mothers (Group C): duration of distress and complications

Name	*Gestation (wk.)*	*Birth weight (grams)*	*Condition at birth*	*Age at onset of distress*	*Duration phase 3*	*Duration phase 2*	*Total duration*	*Complications*
Predominant cardiopulmonary symptomatology								
F. C.	36	2,410	Good	10 min.	24 hr.	40 hr.	64 hr.	Jaundice Bilirubin 21.8 mg. %*
T. O.	28	1,106	Good	15 min.	54 hr.	36 hr.	90 hr.	Vomiting Apnea Death
R. W.	36	4,281	Good	105 min.	0	30 hr.	30 hr.	Jaundice Bilirubin 8.2 mg. %
Predominant neurological symptomatology								
A. C.	39	4,013	Fair	Birth	8 hr.	8 da.	8 da.	Congestive failure Vomiting Seizures Jaundice, bilirubin 16.6 mg. %*
R. J.	36	3,005	Poor	Birth	7 hr.	9 da.	9 da.	Atelectasis Vomiting Apnea Jaundice, bilirubin 17.7 mg. %*
L. V.	37	3,133	Good	20 min.	8 hr.	52 hr.	60 hr.	Jaundice Bilirubin 16.6 mg. %*
L. J.	40	3,015	Poor	Birth	0	6 da.	6 da.	Mild clinical jaundice
P. R.	40	3,770	Poor	Birth	0	11 da.	11 da.	None
Cardiopulmonary and neurological symptomatology of equal prominence								
T. P.	37	2,353	Good	15 min.	24 hr.	4 da.	5 da.	Jaundice, bilirubin 15.7 mg. %
W. R.	36	4,748	Good	8 min.	8 hr.	88 hr.	96 hr.	Cord hemorrhage Jaundice, bilirubin 16.1 mg. %*
G. L.	32	1,346	Good	30 min.	1 hr.	7 da.	7 da.	Apnea Seizures Jaundice, bilirubin 16.7 mg. %*
G. J.	35	2,722	Good	30 min.	0	6 da.	6 da.	Left-sided twitching
T. R.	34	3,459	Good	60 min.	1¼ hr.	16 hr.	17¼ hr.	Mild clinical jaundice
W. G.	39	3,246	Poor	Birth	2¾ hr.	5⅓ hr.	8 hr.	None
B. S.	40	3.586	Good	60 min.	4 hr.	0	4 hr.	None
H. R.	37	3.515	Good	30 min.	0	5½ hr.	5½ hr.	None

*Exchange blood tranfusion.

mittent retractions. In infants whose symptomatology was predominantly cardiopulmonary, the breathing was regular. In infants with predominant neurological symptomatology, the regularity of respiration was frequently disturbed by outbursts of activity, diaphragmatic tremors, or seizures. Under these conditions the one-minute respiratory rate was not constantly increased.

In lower Phase 2 the heart rate was increased. Throughout the remainder of this phase, the heart rate was normal.

Neurological. With the onset of Phase 2, a sudden increase in activity occurred. Reflex responses improved, and the infant opened his eyes. Chewing and smacking movements of the lips became evident. These were the only neurological manifestations of Phase 2 observed in a portion of the infants with predominant cardiopulmonary

symptoms, but in the remainder and in infants with predominant neurological symptoms, the manifestations were as follows: The infant's facial expression became overalert, staring, and/or anxious. Hyperactivity and tremors were prominent. The infant then either progressed directly to Phase 1, or developed the exaggerated reflexes and increased tonus of upper Phase 2. Throughout Phase 2, the predominant autonomic activity was sympathetic.

Phase 1.

Cardiopulmonary. The transition from Phase 2 to Phase 1 was less marked than the onset of Phase 2. Respiratory and cardiac activity gradually assumed the lability characteristic of the neonate.

Neurological. In this phase, activity and neurological behavior approached the normal. The infant's responses (including autonomic nervous system manifestations) varied with stimuli (see Appendix for illustrative case summary).

Eleven of the 16 infants of Group C had clinical patterns characteristic of Phase 3, and 15 had patterns characteristic of Phase 2. The direction of the clinical pattern was not uniform. In 10 patients the direction was toward clinical deterioration followed by improvement (Phases 1 to 2 to 3 to 2 to 1, Phases 1 to 3 to 1, Phases 1 to 2 to 1). In 5, the direction was solely one of improvement (Phases 3 to 2 to 1, Phases 2 to 1). In the remaining infant the clinical direction was Phases 1 to 3 to 2. This infant (T. O.) died following a prolonged period of apnea during the course of Phase 2.

Complications occurred in 12 of the 16 infants of Group C during the period of immediate distress. Complications occurring during Phase 3 were atelectasis (1), and congestive failure (1); during Phase 2, cord hemorrhage (1), vomiting (3), apnea (3), seizures (3), and jaundice (8); and during Phase 1, jaundice (2). Two infants of Group B had mild clinical jaundice (less than 9.0 mg. per cent total bilirubin). No complications occurred in infants of Group A.

The character and sequence of the symptomatology and the type and timing of complications observed in the infants of Group C are similar to those described in infants with prolonged pulsations of the umbilical cord and termed transitional distress (Table III). Because of these similarities, the disturbances of transition observed in these infants of diabetic mothers may also be considered to represent transitional distress.

There were differences in the two groups of infants with transitional distress, however, which were not differences in type or sequence of symptomatology, but differences in the infant's condition at birth and in the total duration of distress. Whereas the condition of one half of the infants with prolonged umbilical cord pulsations was rated as "poor" at birth, 11 of the 16 infants of diabetic mothers included in Group C were considered to be in good condition at birth. In addition, the average duration of transitional distress (Phase 3 and Phase 2) in the 15 surviving infants of diabetic mothers was longer (98 hours) than the average duration of transitional distress in the previously reported group of infants with prolonged umbilical cord pulsations (44 hours).

The signs and symptoms observed in infants of Group C were duplicated in infants of Group B, but the symptomatology of Group B infants was not continuous and followed no definite clinical pattern.

There were 2 deaths in this series, both in Group C. The first infant (T. O.) died during transitional distress as described above. A second infant (G. L.) succumbed to a hospital-acquired infection after apparent recovery from the immediate postnatal distress.

Fetal distress. Evidence of fetal distress was present in 9 of 28 cases (1 of 7 in Group A, 3 of 5 in Group B, and 5 of 16 in Group C). These signs included: meconium staining of the amniotic fluid (3), bradycardia or irregularity of the fetal heart tones (4), and decreased fetal activity (4). Only 1 of the 9 infants with evidence of fetal distress had an uneventful neonatal period.

Antepartum and intrapartum factors.

Complications. The mothers of these infants were all known to have diabetes. The

severity of diabetes in the mothers has been designated in accordance with White's classification.[5] The majority of mothers of well infants (5 of 7) were classified as Class A and B diabetics, whereas the majority of the mothers of infants with transient symptomatology (3 of 5), and transitional distress (11 of 16) were in Classes C and D (Table IV).

Hydramnios occurred in only one of the mothers of Group A infants (Table V). Two of 5 mothers of Group B infants and half of the mothers of Group C infants had hydramnios. Maternal toxemia occurred equally in the three groups. A combination of toxemia and hydramnios was present in 3 of the mothers of Group C infants.

Antepartum complications in addition to diabetes were numerous in all groups (Table VI). Intrapartum complications were less frequent but occurred in all three groups. Only 1 mother in the study had neither ante-

Table III. The symptomatology and complications of transitional distress*

The symptomatology of "transitional distress" of the neonate		*Complications seen during the course of transitional distress*
Cardiopulmonary	*Neurological*	
Phase 1		
Normally labile or periodic breathing	Normal activity	
Physiologic lability of heart rate	Normal reflexes	Jaundice
Phase 2		
	Sympathetic effects	
	Upper	Jaundice
	Reflexes exaggerated	
	Increased tonus	
Irregular respiration	Lower	Seizures and/or apnea
Decreasing respiratory rate	Hyperactivity and tremors	
	Abdominal distention	Vomiting
Transient increase in heart rate	Chewing and smacking	
Rapid regular respiration	Open eyes, anxious expression	Cord hemorrhage
	Visible peristalsis, left to right	
Phase 3		
	Parasympathetic effects	
Respiration—increased rate, moderately labored	Diminished reflexes	
	Inactivity	
Clear loud heart sounds		
Normal heart rate		
Grunting, labored respiration	Poor response to stimulation	Congestive failure
Gasping respiration	Absent reflexes	
Cyanosis	Ileus	Atelectasis
Slow heart rate	Hypotonus	
Apnea neonatorum	Unresponsive to stimulation	
Improvement↑	*Deterioration*↓	

*This outline represents the modification of a previously published table.[1] The symptomatology has been divided into phases under two main groupings, cardiopulmonary and neurological, and the complications developing during each phase of transitional distress have been listed. Since the clinical behavior of infants with transitional distress has been previously compared with the behavior of patients recovering from anesthetic or anoxic depression, the numerical designation of the phases is in keeping with the order generally used to describe the stages of anesthetic or anoxic depression. The highest number (Phase 3) is given to the phase corresponding to the stage of deepest depression.

The Neurological Phase 2 has been divided into lower and upper. Lower Phase 2 includes the early neurological symptoms of recovery, the symptoms which are more commonly evident. Upper Phase 2 includes the exaggerated neurological symptoms which may follow Lower Phase 2 symptomatology.

Table IV. Maternal diabetic status

	Number of infants	Maternal diabetic status*	
		A and B	C and D
Group A infants, no observed distress	7	5	2
Group B infants, transient symptomatology without a definitie clinical pattern	5	2	3
Group C infants, transitional distress	16	5	11

*Classification of White.[21]

partum nor intrapartum difficulties. It is of interest however, that her diabetes was classified as severe (Class D), and that her infant had a prolonged course of transitional distress (see Appendix).

Length of gestation. The median gestation period was essentially the same in all three groups (36 to 37 weeks). The range was 36 to 40 weeks in Group A, 35 to 40 weeks in Group B, and 28 to 40 weeks in Group C.

In Fig. 1, the incidence of transitional distress and mortality are plotted according to the gestational age. The relative number of infants developing transitional distress was approximately the same in those delivered at 35 to 37 weeks as it was in those delivered at 38 to 40 weeks. However, the 3 infants with gestational age of 34 weeks or less all exhibited transitional distress.

Birth weights of the infants ranged from 1,106 to 4,748 grams. The median weights in Groups A, B, and C are essentially the same (3,147; 3,281; and 3,149 grams, respectively). Included in Group C, however, are 2 infants with very low birth weights, one of 1,106 grams (28 weeks) and the other 1,346 grams (32 weeks). These are the 2 infants of the series who died.

Mode of delivery. Ten infants were delivered vaginally and 18 by cesarean section. Transitional distress occurred in 5 of the 10 infants delivered vaginally and in 11 of the 18 infants delivered by cesarean section.

Follow-up. Of the 28 infants described in this report, 21 have been followed for periods ranging from 9 to 22 months at the time of this writing. Two died during the neonatal period and 5 have been lost to study (Table VII). Of the 21 infants available for follow-up, 16 appear to be normal, and 5 have evidences of abnormality on neurological examination. These include: developmental retardation, persistence of temporary reflexes, hypertonicity of both lower extremities, and massive spasms. The 5 infants with possible neurological sequelae, as well as the 2 who died, had transitional distress.

Two infants with congenital malformations are also being followed. One infant has a dextrocardia and severe growth retardation. The other infant has microcephaly and congenital heart disease in association with growth and developmental retardation.

DISCUSSION

The early neonatal period of infants of diabetic mothers is frequently complicated

Table V. Incidence of hydramnios and toxemia

	Number of infants	Maternal status		
		Hydramnios	Toxemia	Hydramnios and toxemia
Group A infants, no observed distress	7	1	3	0
Group B infants, transient symptomatology without a definite clinical pattern	5	2	2	0
Group C infants, transitional distress	16	8	6	3

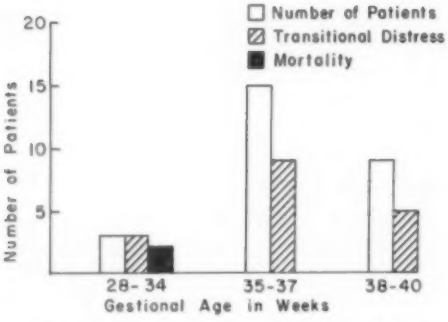

Fig. 1. Incidence of transitional distress and mortality related to gestational age.

by respiratory distress and disturbed activity.[6-13] Of the 28 infants of diabetic mothers described in this paper, 7 appeared well during the early neonatal period, 5 infants had transient symptoms, and 16 (57 per cent) had an orderly sequence of cardiopulmonary and neurological symptomatology. These signs and symptoms and their sequence are similar to the signs and symptoms and to the sequence of transitional distress as previously described.[1] However, the duration of transitional distress in infants of diabetic mothers was more than twice as long as the duration of transitional distress described in infants with prolonged postnatal umbilical cord pulsations.

The signs and symptoms of transitional distress developed in three phases (Table III). With clinical improvement, the infant progressed from Phase 3 to Phase 2 to Phase 1, and in the opposite sequence with deterioration.

A relationship between the severity of maternal diabetic status and perinatal mortality has been well documented.[5, 11, 14, 15] In the present study a similar relationship appears to exist between the severity of maternal diabetes (White's classification)[5] and the presence of distress in the neonate. The manner in which the severity of maternal diabetes affects the outcome of the infant is, however, not clear. A number of authors[5, 6, 10, 16] have suggested that the symptoms seen in infants of diabetic mothers are

Table VI. Mothers with antepartum and intrapartum complications in addition to diabetes

	Number of infants	*Maternal complications*		
		Antepartum	*Intrapartum*	*Antepartum or intrapartum*
Group A infants, no observed distress	7	7	2	7
Group B infants, transient symptomatology without a definite clinical pattern	5	5	3	5
Group C infants, transitional distress	16	14*	6	15

*One mother without antepartum complications was delivered of a 28 week premature infant.

Table VII. Postnatal course; observations ranged from 9 to 22 months

	Number of infants	*Normal at present*	*Neurological abnormalities*	*Neonatal deaths*	*Lost to study*
Group A infants, no observed distress	7	5	0	0	2
Group B infants, transient symptomatology without a definite clinical pattern	5	3	0	0	2
Group C infants, transitional distress	16	8	5	2	1
Total	28	16	5	2	5

secondary to a prolonged period of inadequate placental circulation and/or a period of intrauterine hypoxia. Berglund and Zetterstrom,[16] MacKay,[17] Walker,[18] and Kaiser and Goodlin,[19] have found a decreased oxygen saturation in the umbilical cord bloods of infants born to diabetic mothers. In addition, Kaiser and Goodlin[19] found a marked decrease in pH and an increase in carbon dioxide tension in umbilical cord blood. Similar biochemical disturbances in the cord blood of fetuses and in the circulating blood of infants on delivery have been related to asphyxia in utero by James and co-workers.[20] Since Kaiser and Goodlin[19] found that the pH and pCO_2 in the fetus did not correspond to the pH and pCO_2 in the mother, they postulated the existence of a placental lesion. Anatomic findings in the placenta, although suggestive,[21] have been inconclusive in this regard.[22, 23]

In a previous publication[1] the signs and symptoms of transitional distress were found to resemble the symptomatology observed in older patients recovering from anoxic or anesthetic depressions. Because of this clinical similarity, as well as the high percentage of maternal antepartum and intrapartum complications, the high incidence of fetal distress prior to delivery, the high incidence of difficulty witih onset of respiration, and the early onset of distress (in infants with prolonged postnatal umbilical cord pulsations), it was postulated that transitional distress represented a recovery of the neuraxis subsequent to a depression or drug effect originating in an abnormal intrauterine environment.

In the current study, the single common factor in all cases was the presence of maternal diabetes. Neonatal morbidity tended to occur more frequently in infants born to mothers with a more severe maternal diabetic state (Table IV). In addition to diabetes, many maternal antepartum and intrapartum complications developed. The presence of these complications was responsible for numerous medications and procedures in the obstetrical management. It is possible that distress in these infants reflects not only the severity of the maternal diabetes, but also the superimposed effects of the complications, medications, and procedures.

The incidence of hydramnios and toxemia is high in this study, as has been previously noted in diabetic pregnancies.[24-28] Hydramnios was more frequent in mothers of distressed than in mothers of nondistressed infants, but toxemia appeared to have no relationship to neonatal morbidity.

The distressed infants had essentially the same median weight and gestational age as nondistressed neonates, although 2 small premature infants are included in the distressed group. The method of delivery did not appear to be a major factor in morbidity, as 50 per cent of the infants delivered by the vaginal route and 61 per cent of those delivered by cesarean section had transitional distress.

The majority of the infants of diabetic mothers appeared to be in good condition at birth. Of the 16 infants who developed transitional distress, 5 required resuscitation and had abnormal symptomatology extending from birth. In the remaining 11, abnormal symptoms appeared between 10 and 105 minutes of life. The majority of infants with transitional distress did not have prolonged pulsations of the umbilical cord. Cord pulsations were noted in 2 of the infants with transient symptomatology. Four infants in Group C had prolonged umbilical cord pulsations during Phase 3.

A group of complications have been previously noted to occur during the phases of transitional distress (Table III). In the infants of diabetic mothers, the complications noted during Phase 3 were atelectasis and congestive failure. In Phase 2, the complications were cord hemorrhage, vomiting, apnea, seizures, and jaundice.

Jaundice of varying degrees occurred in 12 of the patients. In 7 patients the total bilirubin levels exceeded 15 mg. per cent during the early neonatal period. With two exceptions, the height of the bilirubin concentration was related to the duration of Phase 3. The duration of Phase 3 ranged from 7 to 24 hours in 6 of the 7 infants with significantly

elevated bilirubin levels. In the seventh infant (1,346 grams) Phase 3 lasted only 1 hour, but jaundice appeared during Phase 2. An additional infant, in whom Phase 3 was longer than 7 hours, was the only one who died during the period of distress. This small premature infant (1,106 grams) died following repeated apneic attacks in Phase 2, without clinical evidence of jaundice.

In many respects, which include severity and duration of maternal diabetes and occurrence of hydramnios, the mothers of infants included in Group B (transient symptomatology without a definite clinical pattern) closely resemble the mothers of infants of Group C (transitional distress). The infants with transient symptomatology showed some of the signs of transitional distress, but the process was not noted to be continuous. It is possible that infants exhibiting transient symptomatology had a milder form of transitional distress.

The management of infants during transitional distress was essentially the same as outlined in a previous report[1] and was dependent on close infant surveillance. Handling was noted to be frequently followed by temporary reversal of recovery. Oxygen was used liberally in Phase 3, and was continued in decreasing concentrations until cyanosis disappeared. Glucose solution (5 per cent dextrose in water) was given intravenously in selected cases during Phase 3, and during upper Phase 2 when symptoms of neural hyperexcitability were exaggerated. Oral feedings were withheld during Phase 3 and upper Phase 2, but administered with caution during lower Phase 2. Sedation of infants exhibiting exaggeration of neural symptoms of upper Phase 2 was employed in 4 cases.

Five of the 28 infants without congenital anomalies have shown evidence of neurological abnormalities at 9 to 22 months of age. These 5 infants had signs and symptoms of transitional distress in the early neonatal period. Retrospective studies[29, 30] have shown the incidence of diabetes to be higher in mothers of infants with cerebral palsy (0.8 to 20 per cent) than the incidence of diabetes in an unselected obstetrical population (0.1 per cent). The high incidence of neurological variations evident in our patients at the present time will require continued follow-up for a true evaluation. However, the present study indicates that the effects of maternal diabetes on the infant may be important not only in the immediate neonatal period, but may have implications for the future development of the child.

SUMMARY

1. The clinical behavior of 28 consecutive liveborn infants of diabetic mothers has been described. Two additional infants born during the study period were excluded because of the presence of congenital anomalies.

2. The patients were divided into three groups on the basis of symptomatology:

Group A No observed distress, 7 cases
Group B Transient symptomatology without definite clinical pattern, 5 cases
Group C Transitional distress (cardiopulmonary and neurological distress), 16 cases

3. The symptomatology shown by the Group C infants occurred in an orderly and predictable sequence. The type of symptomatology, the sequence, and the complications were found to be similar to those previously described in infants with prolonged umbilical cord pulsations and termed transitional distress. It was concluded that the cardiopulmonary and neurological symptoms of infants of diabetic mothers may also be termed transitional distress.

4. Transitional distress in infants of diabetic mothers differed from transitional distress in infants with prolonged umbilical cord pulsations in two respects: the duration of distress was longer, and more of the infants were rated as "good" at birth.

5. Transitional distress may occur with or without prolonged pulsations of the umbilical cord. Only 4 infants in Group C had pulsations of the cord.

6. The severity of maternal diabetes appeared to be the most important factor

related to the presence of distress in the infant.

7. Possible explanations for distress in the infant are discussed. It is suggested that the symptomatology may represent the adverse effects of a severe maternal state together with the superimposed effects of antepartum and intrapartum complications, medications, and obstetrical procedures.

8. The prolonged duration of symptomatology in infants of diabetic mothers reported here may be related to a longer exposure of the infant to an abnormal intrauterine environment.

9. Two of the 28 infants died in the early neonatal period. The neurological follow-up examinations of 5 of the surviving infants were not considered to be within normal limits for their ages (9 to 22 months).

APPENDIX

Case report (Fig. 2). T. P., a 2,353 gram white female, was born to a 23-year-old primigravid, diabetic mother (Class D), at 37 weeks' gestation. Diabetic control was good throughout pregnancy; and, aside from the severity of the diabetic status, the antepartum period was uneventful. The infant was delivered by cesarean section under spinal anesthesia. The Apgar score[31] was 8; and excessive mucus was repeatedly suctioned from the pharynx. Six cubic centimeters of fluid and air were obtained by gastric intubation. The infant was placed in oxygen. She was edematous with puffy cheeks and had the classical appearance of an infant of a diabetic mother. At 15 minutes of age, the respiratory rate was 40 per minute. Expiration was accompanied by an audible grunt. The chest expansion was symmetrical. The heart rate was 148. The umbilical cord was noted to be pulsating at 1 hour after birth and to have minimal oozing at 1 hour and 15 minutes. Visible peristaltic waves were observed at 1 hour.

During the first 24 hours, the respiratory rate remained between 50 and 80 per minute, and respiration was labored and grunting. The heart rate ranged between 130 and 160 per minute. The infant was quiet and inactive. In an oxygen atmosphere of 60 to 70 per cent the color remained good with the exception of peripheral cyanosis.

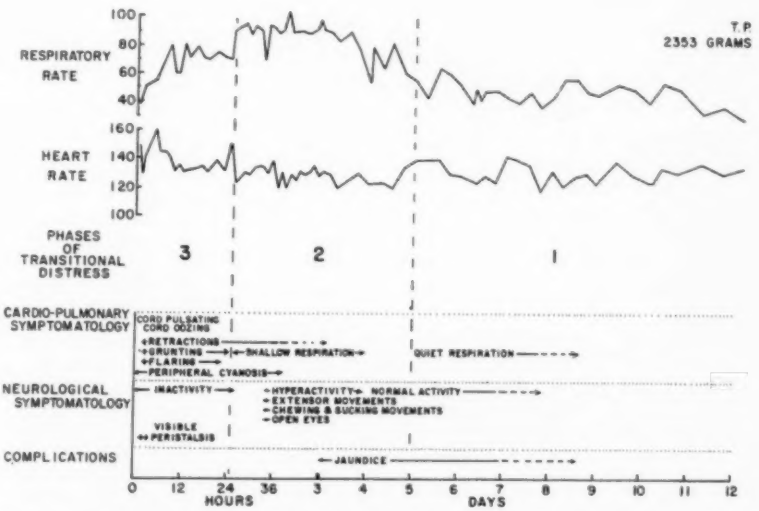

Fig. 2. The clinical course of a 2,353 gram female infant born to a 23-year-old primipara, a Class D diabetic, at 37 weeks' gestation.

At 25 hours, the respiratory rate increased and remained elevated for the ensuing 12 hours. Respiration was shallow and irregular, and subcostal retractions were less marked. A roentgenogram of the chest at this time showed diffuse granularity involving all portions of the lungs. At 32 hours, the infant appeared more alert and the eyes were open. Chewing and sucking movements of the lips were present. Occasional rapid, brief, and bilateral extensor movements of the extremities were noted. An intravenous infusion of 5 per cent glucose in water was begun.

At 38 hours, the infant became hyperactive. Extensor movements of the extremities were accompanied by minimal arching of the back and retraction of the head. These movements were neither periodic nor accompanied by a change in color. Sedation was begun. At 48 hours, the hyperactivity began to diminish and jaundice of a mild degree was noted for the first time. During the third day the respiratory rate gradually decreased and activity became that of the normal neonate. The infant became progressively jaundiced with the total bilirubin concentration reaching 15.7 mg. per cent on the fifth day of life. The respiratory rate approached normal on the sixth day, and oxygen was discontinued. Oral feedings were begun on the seventh day. The course, thereafter, was uneventful. A repeat chest film on the eleventh day was interpreted as normal. Neurological and developmental examinations at 9 months of age revealed no abnormalities.

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A field study in triple immunization (diphtheria, pertussis, tetanus)

Estimation of 3 antibodies in infant sera from a single heel puncture using agglutination techniques

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IN A RECENT report from this laboratory[1] pertussis agglutinin titers were recorded and analyzed for 146 infants subjected to 4 different dosage schedules of plain pertussis vaccine and of combined diphtheria, tetanus, and pertussis antigens (DPT). Sampling was done at various time intervals after the full course. Blood was taken by heel puncture, yielding about 0.1 to 0.2 ml. of serum which was maintained in the frozen state. Initial dilutions of 1:20 in saline were made for the pertussis agglutination tests and the unused portion of these dilutions, averaging about 0.8 ml. in volume, was refrozen and stored for repeat tests if they should be desired. After conclusion of the study, it was decided to attempt to estimate diphtheria and tetanus antitoxin titers on these residual 1:20 dilutions using the sensitive hemagglutination technique. The attempt proved quite successful, since the results may be considered validated by agreement with expectancy relative to the emergence of a direct correlation between serum titers and number of toxoid doses received, and of an inverse correlation between titers and time elapsed between the last dose in a given dosage schedule and the taking of the blood sample. It is the purpose of this paper to present an analysis of these data showing the nature of the correlations and their immunologic implications.

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PRELIMINARY STUDY

The first large-scale field study carried out by these laboratories using the hemagglutination technique was the estimation of diphtheria antitoxin levels in the prebooster and postbooster serum samples of 145 boys aged 13 to 18 years, attending Exeter Academy. Each of these sera was also assayed for

diphtheria antitoxin by the rabbit intradermal method, thus providing a measure of reliability of the hemagglutination method with respect to diphtheria. At the conclusion of the laboratory work, all four values were available for each of 140 subjects, namely, the rabbit intradermal and hemagglutination values for both prebooster and postbooster samples.

The primary objective of the above study was to assess the effectiveness of very low doses of toxoid for mass booster immunization. Two agents were used, each in about half the subjects. One was Tetanus and Diphtheria Toxoids, Combined, for Adult Use, Lot KL5A, which contained 1 flocculating unit (Lf) of diphtheria and 5 Lf of tetanus toxoid in the 0.5 ml. injection. The other was Tetanus and Diphtheria Toxoids, Combined, for Booster Use, Lot KTA1, which contained 1 Lf of each toxoid in the 0.5 ml. injection. Aluminum adjuvants were not present in these materials. The rationale of this treatment was discussed by Ipsen.[10] Blood was taken by venipuncture before and three weeks after a single subcutaneous injection of 0.5 ml. of one or other of these materials.

The details of the hemagglutination technique are described below in the pediatric study.

The results of the Exeter study are shown graphically in Figs. 1 to 4. Figs. 1 and 2 show for pre- and postbooster samples, respectively, the frequency of subjects with particular estimates by both techniques. The least squares lines and plus and minus one standard deviation have been drawn through these frequencies. These graphs show a number of interesting features. The diagonal line represents a slope of one and corresponds to identity of values for the two methods. The actual slopes, 0.55 and 0.52 for pre- and postbooster data, respectively, correspond to lines which are pivoted from these diagonals near the center of the graph so that levels lower than about half a unit tend to be depressed by the hemagglutination method, and greater levels tend to be exaggerated. The high levels of the postbooster samples, as would be expected, have smaller scatter than the prebooster samples. Finally, the values of the correlation coefficients between corresponding estimates by the two methods are high and significant, namely, ±0.77 and ±0.81 for

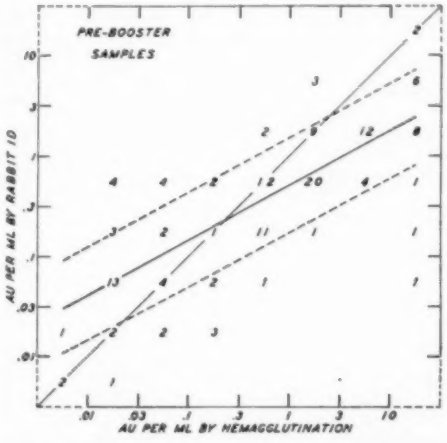

Fig. 1. The correlation between the rabbit intradermal and the hemagglutination methods of estimating serum diphtheria antitoxin levels. The numbers refer to the frequency of subjects whose prebooster serum samples showed particular levels by each method.

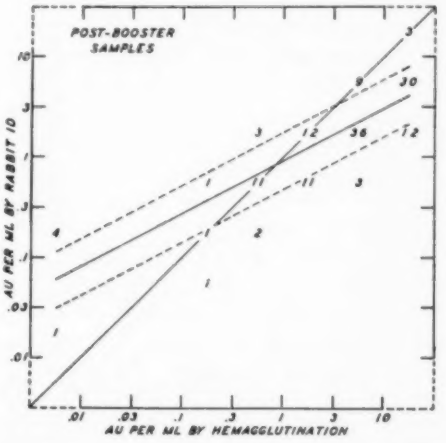

Fig. 2. The correlation between the rabbit intradermal and the hemagglutination methods of estimating serum diphtheria antitoxin levels. The numbers refer to the frequency of subjects whose postbooster serum samples showed particular levels by each method.

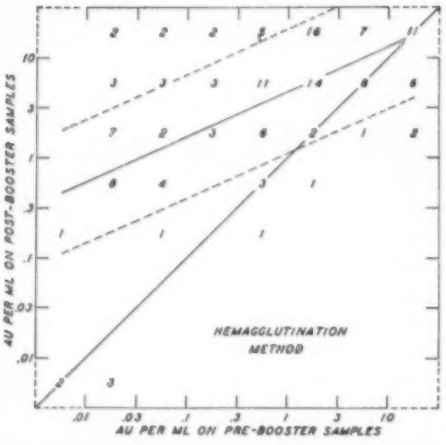

Fig. 3. The effectiveness of a diphtheria toxoid booster dose as determined by the hemagglutination test for antitoxin on human serum. The numbers refer to the frequency of subjects whose postbooster level reached a particular value in relation to their prebooster level.

pre- and postbooster samples, respectively ($P << 0.001$).

Figs. 3 and 4 show, for the hemagglutination and rabbit intradermal methods, respectively, the frequency with which postbooster levels reached a particular value in relation to their respective prebooster level. All subjects whose levels were boosted would of course appear in the triangle above the diagonal. The graph for the hemagglutination method (Fig. 3) shows that 71 per cent were boosted, 19 per cent unchanged, and 10 per cent had lower values. Corresponding percentages for the in vivo method were 75 per cent boosted, 24 per cent unchanged, and 1 per cent lower (Fig. 4). Comparing the space between the dotted lines representing the standard confidence limits, it is apparent that the error of the hemagglutination method is the greater. By calculation, the standard error was 37 per cent greater. The similarity of slopes of the least squares regression lines, however, shows that the two methods are measuring the same variate, although with different precision. These slopes are 0.44 and 0.40 for hemagglutination and for the rabbit intradermal test, respectively.

Conclusions from the preliminary study. Although the precision of the hemagglutination method is not as great as that of the rabbit intradermal method, there is good correlation between them. Correspondence between the methods is best in the approximate range of 0.1 to 3.0 units per milliliter. Above 10 units per milliliter, by the in vivo method, the hemagglutination values may be considerably greater. The advantages of the method are: (1) its high sensitivity, which makes possible estimates from samples too small to be assayed in any other way, and (2) the economy of time and animals in large volume testing for which it is especially suited, since group differences in comparative group studies are more important than absolute individual values, and demand less precision.

THE PEDIATRIC STUDY

Immunizing preparations. Two kinds of preparations were used, namely, plain pertussis vaccine and DPT. Detailed descriptions of these materials were given in the report mentioned.[1]

Dosage schedule. Four dosage schedules were used as shown in Table I. The ration-

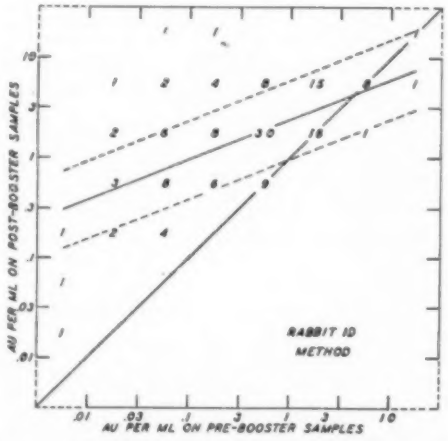

Fig. 4. The effectiveness of a diphtheria toxoid booster dose as determined by the rabbit intradermal test for antitoxin on human serum. For comparison with Fig. 3.

Table I. Composition of treatment groups

Group	No. of children	Dosage schedule	Schedule breakdown		Interval between last injection and blood sample (months)	
			No. of toxoid doses	No. of pertussis doses	Mean	Range
I	51	3 doses of DPT	3	3	3.3	1-48
II	31	3 doses P + 2 doses DPT	2	5	2.3	1-15
III	17	As I + a booster DPT	4*	4*	3.1	1-21
IV	14	As II + a booster DPT	3*	6*	1.8	1-11

*Last dose a booster (a year or more after the basic course).

ale of these schedules was explained in detail in the previous study[1] and was concerned mainly with the efficiency of early pertussis immunization. All doses of DPT were 0.5 ml. The course of plain pertussis consisted of 0.5 ml. + 1.0 ml. + 1.0 ml.

The distinction between a booster and a basic injection in the present context is that a booster was given a year or more after the basic course, whereas the interval between basic injections was 3 or 4 weeks, except that the interval between a plain pertussis series and a DPT series was 2 to 4 months.

Composition of the study groups. It was considered that unbiased information could be obtained from the data only if the analysis was limited to those subjects for whom serum titers were available for all three antibodies. This requirement was fulfilled by 113 children, or 77.3 per cent of the total. Their distribution among the four treatment groups is shown in Table I.

Blood samples. Blood was taken by heel puncture in a micro tube, yielding about 0.1 to 0.2 ml. of serum. From most children only one sample was taken, so that the study is concerned with group response rather than individual responses. Because of the circumstances of a private practice, blood samples had to be taken as occasion arose, so that the interval from the last injection of vaccine to the sampling varied considerably, as it appears in Table I where the mean and range are given.

MATERIALS AND METHODS

Hemagglutination titration for diphtheria and tetanus antitoxin. The method to be outlined was borrowed extensively from the several methods described in the literature which, for the most part, differ only in minor respects.[2-6] The methods described by Boyden[3] and Stavitsky[2] were especially useful.

Commercially obtained sheep blood in Alsever's solution was suspended in ten volumes of sterile saline solution and the cells were washed by centrifuge three times at 2,000 r.p.m. for 5 minutes. One milliliter of the packed cells was suspended in 40 ml. buffered saline,[2] pH 7.2, to obtain a 2.5 per cent suspension.

On the day of the assay the cells were tanned by addition to the above suspension of an equal volume of a 1:100 dilution of a stock 0.4 per cent solution of reagent grade tannic acid in saline. The exposure was at room temperature for a period of 10 minutes, followed by 10 minutes of centrifugation at 1,500 r.p.m. and two washings with pH 7.2 buffered saline. The treated cells were then resuspended in saline to 2.5 per cent.

Separate portions of the tanned cells were sensitized to diphtheria and tetanus toxoids with dilutions of purified, concentrated antigens. The diluent in this case was saline buffered to pH 6.4.[2] The exposure of the cells to toxoid was at the 30 Lf per milliliter level for either antigen. This was obtained by adding 4 volumes of 37 Lf per milliliter toxoid to one volume of 2.5 per cent suspension of tanned cells. Exposure was at room temperature for 10 minutes followed by 10 minutes' centrifugation at 1,500 r.p.m. The cells were washed once and resus-

Table II. Pediatric study: diphtheria, tetanus, and pertussis antibody levels determined from single heel puncture blood samples of 113 infants obtained at various time intervals after immunization by 4 different dosage schedules

Sampling interval (months)	*Antibody levels**			*Sampling interval (months)*	*Antibody levels*		
	D	*T*	*P*		*D*	*T*	*P*
Schedule I							
1	3.2	50.	0	3	0.8	6.4	2.8
1	0.8	1.6	0	4	0.8	1.6	0
1	26.	26.	1.6	4	6.4	13.	1.6
1	0.8	1.6	1.6	4	0.4	0.4	1.6
1	0.8	3.2	1.9	4	1.6	1.6	2.2
1	6.4	6.4	1.9	4	0.8	0.8	2.5
1	1.6	1.6	1.9	4	13.	3.2	2.8
1	0.8	0.8	1.9	5	1.6	0.8	2.2
1	3.2	13.	2.2	5	0.8	0.8	0
1	13.	13.	2.2	6	0.8	0.8	1.6
1	1.6	1.6	2.2	6	<0.4	0.8	1.9
1	3.2	1.6	2.2	6	0.4	0.4	1.9
1	100.	3.2	2.2	6	1.6	1.6	2.2
1	26.	13.	2.5	9	0.4	0.8	1.6
1	13.	26.	2.5	13	<0.4	0.4	2.2
1	1.6	3.2	2.5	13	<0.4	0.4	0
1	>100.	3.2	2.5	16	0.4	1.6	0
1	6.4	1.6	2.5	16	0.8	0.8	1.9
1	<0.4	1.6	2.8	17	0.8	1.6	2.2
1	6.4	13.	2.8	20	0.4	0.4	1.6
1	13.	13.	2.8	30	<0.4	1.6	1.6
2	<0.4	0.4	0	34	6.4	13.	1.6
2	<0.4	1.6	1.9	42	6.4	3.2	1.6
2	3.2	6.4	1.9	43	0.8	0.8	1.9
2	3.2	3.2	2.5	48	0.4	0.8	0
3	0.8	1.6	2.2				
Schedule II							
1	0.4	0.4	1.6	2	3.2	1.6	2.5
1	13.	6.4	2.2	2	3.2	0.8	2.8
1	26.	>50.	2.2	2	3.2	0.8	3.1
1	1.6	0.8	2.2	2	<0.4	0.4	3.1
1	<0.4	3.2	2.5	3	0.4	0.8	1.6
1	6.4	3.2	2.5	3	0.8	0.8	2.2
1	6.4	1.6	2.5	4	0.4	<0.2	2.2
1	1.6	0.4	2.5	5	0.8	0.8	2.2
1	0.8	0.8	2.5	5	1.6	0.8	1.9
1	<0.4	0.4	2.5	11	<0.4	0.2	1.9
1	0.4	0.4	2.5	11	<0.4	0.2	2.2
1	3.2	0.8	2.8	12	<0.4	<0.2	2.2
1	0.8	0.8	2.8	12	<0.4	0.8	2.5
1	13.	1.6	3.1	13	0.4	0.4	1.9
2	50.	26.	1.6	15	0.8	0.8	1.9
2	<0.4	0.8	2.2				
Schedule III							
1	6.4	13.	2.2	5	26.	26.	1.9
1	50.	25.	2.2	6	12.	25.	2.2
1	50.	13.	2.8	6	13.	50.	2.2
1	25.	50.	3.1	7	6.4	6.4	2.2
1	13.	13.	2.5	8	25.	13.	2.2
1	13.	>50.	2.5	9	6.4	6.4	2.2
1	3.2	>50.	2.5	13	0.4	0.2	2.5
2	50.	25.	2.5	21	0.4	3.2	0
4	25.	25.	2.5				

Table II—Cont'd

Sampling interval (months)	*Antibody levels**			*Sampling interval (months)*	*Antibody levels*		
	D	*T*	*P*		*D*	*T*	*P*
Schedule IV							
1	50.	50.	1.9	1	13.	>50.	3.1
1	13.	13.	1.9	2	25.	13.	2.5
1	1.6	13.	2.2	3	6.4	6.4	2.8
1	1.6	6.4	2.5	3	13.	13.	2.5
1	13.	6.4	2.8	4	3.2	50.	1.9
1	25.	50.	2.8	4	13.	13.	2.5
1	25.	25.	3.1	11	<0.4	0.4	2.2

*Diphtheria and tetanus antitoxin levels are recorded in units per milliliter of serum as estimated from the hemagglutinin titers. Pertussis antibody levels are recorded as the logarithm of the agglutinin titers.

pended to 2.5 per cent in a 1:250 dilution of normal rabbit serum (NRS) which had been inactivated at 56° C. for 30 minutes and filtered.

The diphtheria and tetanus hemagglutination tests were performed the same day on each unknown serum, usually with identical dilutions for the two tests. Sera to be tested were inactivated in the manner described above for the rabbit serum (NRS). Dilutions were made in saline containing 1 per cent NRS. Samples of standard diphtheria and tetanus antitoxin were run with each batch of unknowns. Tubes containing only cells and diluent were run to control specificity. Twofold serial dilutions of all samples were made, leaving 0.5 ml. of each in the 12 by 75 mm. tube. Then 0.05 ml. of the tanned, sensitized cells was added, the racks shaken and allowed to stand 2 hours at room temperature. Tubes were read according to the recommendations of Salk,[9] and recorded as positive or negative with respect to agglutination. The last positive tube was designated the end point tube and was considered to have the same unitage per milliliter as the end point tube of the known standard antitoxin which was run with each series. The unitage of the unknowns was thus calculated by applying the dilution factor and constituted the antitoxin level as estimated by the hemagglutination method.

Pertussis agglutinin titers. This procedure was described in detail in a previous paper.[1]

RESULTS AND DISCUSSION

Table II gives the levels of the three antibodies obtained from the heel puncture sample of each of the 113 subjects, together with the time interval between completion of the particular schedule and the blood sampling. The diphtheria and tetanus titers are given in terms of the units per milliliter as estimated by hemagglutination; the pertussis titers are in terms of the logarithmic reciprocal agglutinin titers. The pertussis titers were not repeated, but were taken from the previous study.[1]

Analyses of variance of the responses to each antigen as a function of the log time interval between immunization and sampling were carried out. As in the previous study involving pertussis alone, significant negative regressions of response on elapsed time were found for all three antigens. Fig. 5 shows the regression lines for a 10 month interval for each antigen and dosage schedule. The diphtheria and tetanus antitoxin titers declined approximately 75 per cent in 10 months, and the pertussis antibody about 50 per cent. It is also clear from Fig. 5 that the number of doses of toxoid, and whether or not the last dose was a booster, had a marked effect on the response, as was to be expected. It is noteworthy that the diphtheria and tetanus patterns were so similar. It is also of interest that 5 doses of pertussis without any booster was equivalent to 4 doses with the booster interval. Similarly, 3 doses of toxoid gave significantly

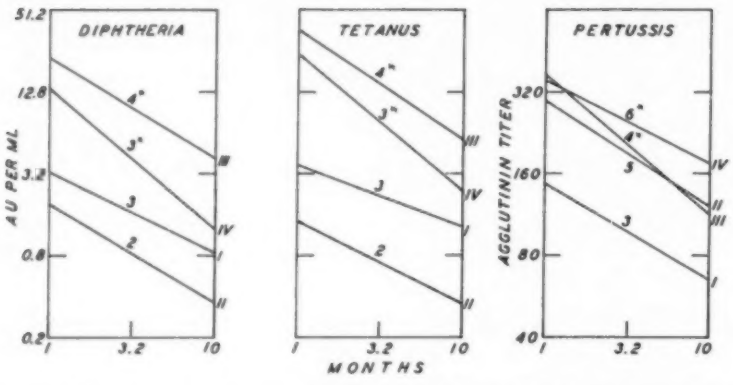

Fig. 5. The mean rate of change of antibody levels following the last immunizing dose in the triple immunization of children as determined by agglutination techniques applied to single heel puncture samples. The number of doses of each antigen received is indicated at the centers of the lines representing each dosage schedule. The asterisk indicates that the last dose was a booster dose. Numbers of subjects per dosage schedule may be ascertained in Table I.

different responses depending on whether the third dose enjoyed the booster interval, and this difference approximated the equivalent of one additional dose.

The scatter of antibody levels about the regression lines for each dosage schedule, based on the standard errors of the regressions, was in the following ratio: tetanus 1.0, diphtheria 2.5, pertussis 1.8. This suggests greater precison for the tetanus antitoxin assay than for the other two. In fact, the standard error in the case of tetanus was sufficiently small that the nonparallelism of the lines must be considered real by statistical test, whereas nonparallelism for the other antibodies was insignificant. With respect to the diphtheria component of the sera, the preliminary study indicated the regression of rabbit intradermal titers on hemagglutinin titers to be considerably less than unity. Thus hemagglutinin titers appear inflated relative to intradermal titers at higher levels and could account for some of the apparent waning of immunity with time. However, there is no a priori reason for considering either system as presenting a more faithful picture than the other in regard to resistance to infection. Indeed, on the basis of Scheibel's[6] work, the evidence favors the hemagglutination method in this respect. She has shown: (1) that there is good agreement between the resistance of guinea pigs to diphtheria toxin and the hemagglutination titers of their sera, and (2) that the avidity of antitoxins affects the hemagglutination titers less than the intradermal titers.

It is of interest to raise the question whether any of the toxoid responses were "crowded out" in Groups II and IV by the initial treatments with plain pertussis vaccine. The data were examined in different ways from this viewpoint but no evidence of a crowding-out effect could be found. On the other hand, the possibility of some degree of inhibition of the Group II response from this cause could not be excluded. A dosage schedule involving the toxoids alone would have been necessary for an unequivocal answer to this question, but this was not an objective of this study.

In recent years a number of studies[2-8] of the hemagglutination technique, mainly for assay of antidiphtherial sera, have been published. Most of these studies have followed the pattern of our preliminary study, namely, to test the correlation between hemagglutination titers and titers obtained by classical methods, usually the rabbit in-

tradermal method. Studies in which these methods have been put to practical use have been quite rare, however. The present validation of these techniques in a field study involving a comparatively small population group suggests considerable potential usefulness for such highly sensitive methods in multiple immunization trials where the freedom to draw blood samples in milliliter amounts has always been a difficult obstacle, especially in pediatric practice.

SUMMARY

A useful field study in multiple immunization was described, which was carried out within the routine of a private pediatric practice with a minimum of inconvenience to the child. This was made possible by the high sensitivity of the agglutination techniques whereby reliable antibody titers to three antigens, diphtheria and tetanus toxoids and pertussis vaccine, were obtained for each treatment group from single heel punctures. The methods were described and the evidence of their validity discussed.

The validity of the hemagglutination method is supported by the facts that the results show clear dependence on the number of antigen doses injected and a reasonable decline in time after the last antigen injection.

Acknowledgments are due to Dr. James T. Heyl and his associates at Phillips Exeter Academy who carried out the immunizations and took the blood samples, and to Dr. R. William Provenzano who conducted the field work in his pediatric practice. We also wish to express appreciation to Miss Leslie H. Wetterlow for her careful handling of the original blood samples, which was essential to this study, and for the results of the pertussis agglutination tests.

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Metaphyseal dysostosis

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ABNORMALITIES in the conversion of cartilage matrix to bone may occur in the primary cartilage dysplasias (chondrodysplasias), in diseases involving cartilage growth (e.g., hypothyroidism), or in conditions involving the deposition of calcium and phosphorus in bone matrix (rickets or osteomalacia). In general, certain radiographic and clinical features distinguish the cartilaginous dysplasias while characteristic biochemical and radiographic changes lead to the diagnosis in the osteomalacias.

The present report concerns 3 patients in whom the radiographic findings were inconclusive but suggestive of rickets while the biochemical findings revealed no evidence of a defect in the metabolism of calcium and phosphorus.

CASE 1

R. D. H. was first seen in 1956 at the age of 3½ years (Fig. 1) because of dwarfism and bowed legs. History disclosed that the child was normal at birth and was not thought to be in any way unusual until he began to walk at approximately 14 months of age. It was then noted that his legs were bowed and that he was shorter than his older sibling had been at the same age. Previous to this time multiple examinations by physicians had failed to reveal any abnormality.

At the age of 2½ years he was taken to a physician who stated that the child had rickets and started him on a concentrated vitamin D preparation, 50,000 units daily. This was continued for 11 months without clinical evidence of toxicity or visible influence upon the child's bowed legs. The patient was then seen at another hospital where operative correction of the hip was suggested. This procedure was declined by the parents and no further treatment was carried out. It was noted at this time that the urinary Sulkowitz reaction was strongly positive; the urine specific gravity was 1.018, and the urine pH varied from 6.5 to 7.5. Serum chemical determinations included: blood urea nitrogen, 9 mg. per cent; calcium, 11.9 mg. per cent; phosphorus, 4.3 mg. per cent; chloride, 112 mEq. per liter; total serum protein, 7.0 (albumin 3.2) Gm. per cent, and total carbon dioxide

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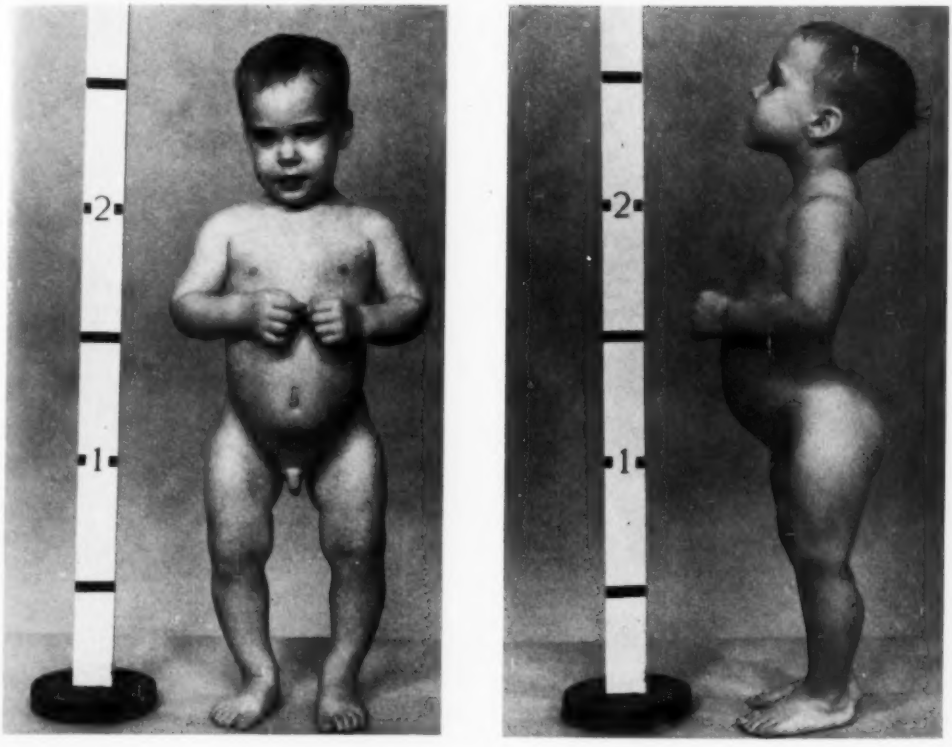


A B

Fig. 1, *A* and *B*. (Case 1.)
Frontal and lateral views of the patient demonstrate the slight enlargement of the wrists and bowing of the legs, as well as the accentuation of the lumbar lordotic curve.

18 mEq. per liter. The blood hemoglobin was 13.7 Gm. per cent and the white blood count was 7,200 per cubic millimeter with a normal differential.

Further examination of the past history revealed that the child had always been physically vigorous, showed no tendency to episodes of dehydration or acidosis with infections, and except for the short stature and bowed legs was a normal child. He was able to run and jump; his intake of water was normal, and he tolerated periods of water restriction well. Stools were normal in form, color, and frequency. He had no history of genitourinary infections. The pattern and schedule of tooth eruption had been normal, and at the age of 3½ years he had lost no teeth. There was no history of fracture. The parents felt that the overall health of the child had been excellent.

The mother's gestational and delivery history was normal. The birth weight was 6 pounds, 11 ounces, and the neonatal period was uncomplicated. Feeding, growth and development, and weight gain had been entirely within normal limits. He had received the usual immunizations and had had several childhood diseases plus the usual upper respiratory infections without unusual difficulty.

The mother was 26 years old, living and well. The father (Case 2) was 41 and living; he had always been in good health, but he too had been short of stature and had had

A

C

B

Fig. 2, *A*, *B*, and *C*. (Case 1.)

***A*,** Radiographs of the lower extremities show bowing of each femur and tibia, as well as irregularity and splaying of the distal femoral metaphyses and proximal tibial metaphyses. Similar irregular mineralization is seen in the proximal femoral metaphyses. The epiphyses are essentially normal.

***B*,** Radiograph of the wrist shows enlargement of the distal radius and ulna with irregular mineralization at the epiphyseal line, but dense provisional zones of calcification.

***C*,** Radiograph of the humerus shows this structure to be short and broad with irregularity of the proximal metaphysis and some widening of the epiphyseal line.

bowed legs since infancy. One brother of the patient, aged 9 years, is normal.

Physical examination of the patient revealed a height of 32 inches, weight of 28¾ pounds; he was of average size for 2 years at a chronologic age of 3½ years. Frontal occipital circumference was 19 inches, chest 20½ inches, and blood pressure 115/70. His general appearance (Fig. 1) was that of a well-developed and well-nourished child of short stature with obviously bowed legs, who did not appear either acutely or chronically ill. It was noted that the trunk appeared long in proportion to the legs and there was accentuation of the lumbosacral lordosis. The child was happy, alert, cooperative, and appeared to be quite normal mentally.

There were no abnormalities in the shape of the head or appearance of the facies. The 20 teeth present were in good condition. The extremities were short with marked genu varum and pes planus; there was some enlargement of the knee and wrist joints; the gait was somewhat waddling. The upper/lower ratio was 1.5, which is characteristic of a child 18 months of age.

Roentgenographic examination of the skeletal system (Fig. 2) showed the major abnormality to be confined to the metaphyseal ends of the long bones. In these areas the cartilaginous plate was slightly widened and there was considerable irregularity of the metaphyses. The epiphyses were well formed and essentially normal in appearance. The provisional zones of calcification were irregular but dense. These changes were most pronounced at the proximal and distal femoral metaphyses but were also very prominent at the proximal and distal portions of the tibias, at the proximal metaphyses of the humeri, and at the distal metaphysis of each radius and ulna. There was flaring of the distal ends of the ribs similar to that seen in rickets. The over-all mineralization of the skeleton was considered to be within normal limits. Each of the long bones of the upper and lower extremities was slightly shortened and definitely broadened; in addition there was considerable bowing of each femur and tibia, especially pronounced in the femurs. The skull was of normal appearance and no abnormality of the vertebral column was present.

It was felt that the bone changes represented either healing rickets or chondrodysplasia. Dental radiographs revealed normal dental development and no evidence of enlarged pulp chambers. There was no evidence of demineralization of the jaw or changes suggestive of metabolic disturbances in the permanent tooth buds. The dental consultant felt these findings were normal and incompatible with a diagnosis of rickets.

Slit lamp examination of the cornea failed to reveal any crystals; examination of the urine showed no reducing substance.

Because of the moderately reduced values for plasma bicarbonate and moderately elevated values for plasma chloride in the presence of a neutral to only slightly acid urine, the patient's ability to form titratable acid and ammonia under circumstances of chloride and phosphate loading was studied. The results of these tests indicated a normal ability to make titratable acid and ammonia and to produce a urine in the pH range of 4.5 to 5.0.

The possibility that this child had resistant rickets had been raised, and since he had been on vitamin D for some time the vitamin D therapy was discontinued for approximately 3 months and the renal tubular handling of phosphorus was measured. Here again a normal rate of reabsorption of phosphorus by the renal tubule was demonstrated and the mechanisms of phosphorus conservation appeared to be normal both at low serum phosphorus levels and following phosphorus loading.

Serial radiographic examinations of the long bones during a 3 month period on 200,000 units of vitamin D daily failed to reveal any change in the roentgenographic appearance of the metaphyseal and epiphyseal areas. During this period the serum calcium and phosphorus values were carefully followed, and when the calcium value exceeded 11.5 mg. per cent (12.2 mg. per

A

B

Fig. 3, *A* and *B*. (Case 2.)
Short stature due largely to marked shortening of femurs but there is some shortening of legs too. Muscle strength is excellent.

cent) further trial of vitamin D as a therapeutic agent was abandoned. It was felt that the laboratory studies plus the clinical experience effectively ruled out vitamin D resistant rickets and renal tubular acidosis as a cause of the "rickets-like" changes in the patient's epiphyseal areas.

CASE 2

C. H. H., a 41-year-old white male, the father of Patient 1, was first seen at the time his son was brought in for studies. He appeared clinically to be the adult counterpart of his son. History revealed that he had always been a vigorous individual and

felt that he was at least as agile and vigorous as his contemporaries. A diagnosis of "poliomyelitis" had been made in early childhood because of short, bowed legs following a period of high fever. He gave no history of fractures, weakness, bulky stools, or genitourinary tract disease, and he denied unusual episodes of vomiting and dehydration in infancy. He believes that he was an "unusually healthy" child and that short arms and legs were his only abnormality. There was no known history of similar deformity in his parents or grandparents and no familial history of endocrine or metabolic disease.

Physical examination revealed a height of 54 inches and a weight of 145 pounds. He was of stocky build and appeared physically vigorous (Fig. 3). The only abnormalities noted were marked bowed legs with shortening of the extremities and a moderate enlargement or prominence of the joints of the wrist, knee, and ankle. The gait was stable but waddling. Laboratory studies revealed normal values for calcium, phosphorus, sodium, potassium, blood urea nitrogen, and carbon dioxide. The routine urinalysis was normal.

Radiographs of the skeleton (Fig. 4) showed all long bones to be shortened and slightly increased in thickness. The epiphyseal lines were fused and there was normal density. There was lateral bowing of each femur, as well as slight anterior bowing of each tibia and fibula.

CASE 3

G. D. D. (Fig. 5) was referred for evaluation at the age of 10 months because of clinical and roentgenographic evidence of rickets unassociated with hypophosphatemia, hypocalcemia, and elevated serum alkaline phosphatase.

The history disclosed that the patient was born at term after an uncomplicated gestation. Labor lasted 17 hours and delivery was accomplished only after forceps rotation of the head. The infant weighed 7 pounds, 7 ounces. He appeared vigorous at birth, but at 2 weeks of age the attending physician suspected the "head was a little large" and measured it frequently thereafter. At 7½ months radiographic examination of the head was performed because of suspected hydrocephalus, but the parents were told that no hydrocephalus was found. The parents also felt that the forehead was "prominent." The feeding history was good, and multivitamin supplements were given regularly. The patient gained weight regularly and adequately. Motor development was well within normal limits. He received the usual immunizations without incident and had experienced no significant infectious diseases or injuries.

At the age of 9½ months it was noted that the extremities were short relative to the trunk and that gain in length was not paralleling gain in weight. Roentgenographic examination of the extremities performed elsewhere led to a diagnosis of rickets.

Physical examination showed the circumference of the head to be 19¼ inches; chest, 15½ inches; abdomen, 18 inches; length, 27½ inches; and weight, 17 pounds, 7 ounces. The upper/lower ratio was 1.8, a ratio below that of the normal newborn infant. Blood pressure was 110/60, and the pulse rate was 120. The head was somewhat triangular in shape with a prominent forehead. The anterior fontanel was patent, measuring 3 by 3 cm. The posterior fontanel could be located but was virtually closed. There was a moderate flaring of the lower chest and a decrease in the anteroposterior diameter of the thorax. The abdomen was moderately prominent but examination was otherwise normal.

The patient could stand with support. There was an accentuation in the usual degree of bowed legs, and the legs were relatively short as compared to the trunk.

Laboratory studies revealed blood urea nitrogen 13 mg. per cent, serum inorganic phosphate 5.4, alkaline phosphatase 5 Bodansky units, calcium 9.8 mg. per cent, and total carbon dioxide 23 mEq. per liter. The urine pH was acid and a random specific gravity determination was 1.021.

A

B

C

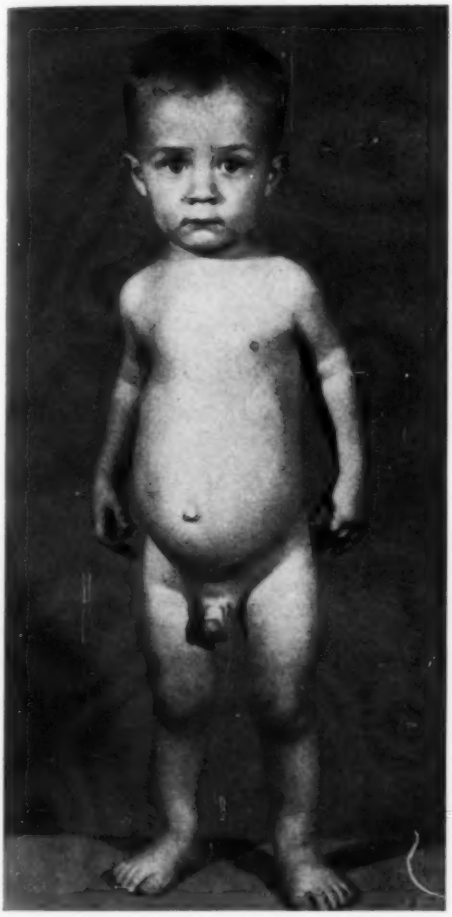
Fig. 4, *A*, *B*, and *C*. (Case 2.) Skeletal radiographs of an adult with metaphyseal dysostosis.

A, The right humerus is abnormally short and there is increased prominence of the deltoid tuberosity with some loss of the normal modeling process.

B, Bilateral coxa vara with shortening of each femur and loss of normal modeling. The femoral necks are also abnormally short and a small exostosis projects medially from the symphysis into each obturator foramen.

C, Relatively normal length of each tibia and fibula as compared to the loss of length of each femur. Again, there is absence of normal modeling.

Roentgenographic studies (Fig. 6) showed changes resembling both achondroplasia and metaphyseal dysostosis. The findings in the chest and pelvis more closely resembled achondroplasia. The ribs were abnormally short, producing an unusually short anteroposterior diameter of the chest. The pelvic changes consisted of marked underdevelopment of the inferior portion of each ilium similar to the deficiency in this area com-



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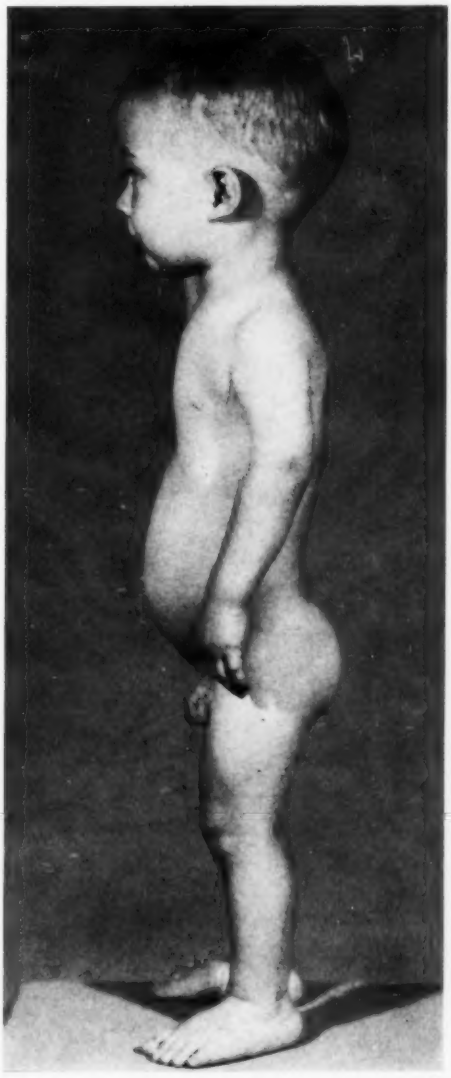


B

Fig. 5, *A* and *B*. (Case 3.)
Photographs taken at the age of 20 months showing moderate head and chest deformity. At this time the patient was 30½ inches tall and weighed 27 pounds; the upper/lower ratio was 1.8. Skeletal x-rays showed no change from those taken at age 10 months (Fig. 6).

monly seen in achondroplasia. There was enlargement of each acetabulum and irregular mineralization of each iliac crest, as well as of each acetabular roof. The remainder of the skeleton, however, resembled the rickets-like changes of metaphyseal dysostosis. There was separation of each capital femoral epiphysis from the adjacent metaphysis and similar separations were noted for the distal femoral epiphyses. There were areas of irregular calcification at the distal ends of the metacarpals, the distal ends of each elbow, and at the ends of the bones of the forearm. The distal humeral metaphyses showed some splaying, as did each femur and the proximal end of each tibia. The

A

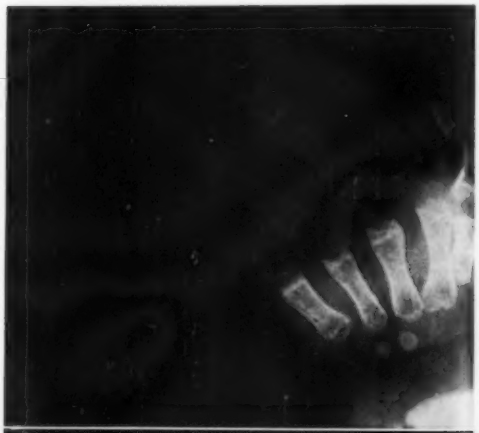
Fig. 6, *A*, *B*, *C*, and *D*. (Case 3.)

A, Radiograph of the lower extremity shows widening of the proximal tibial and distal femoral metaphyses with irregularity of the metaphyses and widening of the epiphyseal line. Provisional zones of calcification are dense.

B, Radiograph of the pelvis shows marked irregular mineralization involving the acetabula and the iliac crests. In addition there is irregularity of the proximal femoral metaphyses and considerable underdevelopment of the lower portion of each ilium.

C, Radiograph of the hand shows irregularity of the distal ends of each metacarpal, as well as shortening of these structures.

D, Radiograph of the upper extremity shows irregularity and splaying of the distal humeral metaphysis and similar findings involving the proximal portion of this structure. There are similar, but less advanced, changes at the distal ends of the radius and ulna.



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mineral content of the skeleton appeared adequate and the provisional zones of calcification were of normal density. The spine was normal and showed no features of achondroplasia.

DISCUSSION

The 3 patients presented here manifested a type of chondrodysplasia in which the defect appears primarily in the metaphyseal area.

In 1934, M. Jansen[1] described a similar patient. Later Fairbanks,[2] reviewing studies on Jansen's patient, commented that there was "no suggestion of a columnar arrangement of the cartilaginous metaphyses as in dyschondroplasia" nor was there epiphyseal mottling. He also noted that the histologic features of the metaphyses were similar to those seen in "rachitis." Evans and Caffey[3] have made a similar comment describing a metaphyseal biopsy specimen from one of their own patients: "The zone of preparatory cartilage was thicker than is usually seen . . . and the cells were not arranged in orderly columns . . . but occurred in oval nests. A thin zone of provisional calcification was present . . . and beyond this, thin bone trabeculae which possessed osteoid tissue at their periphery where seen." Similar cases have also been described by Cameron and colleagues,[4] Lenk,[5] and Maroteaux and Lamy.[6]

In the case reported in 1958 by Evans and Caffey,[3] attention is called to the ease with which the roentgenographic findings in the metaphyses may be confused with active rickets. The medical course of the case they report is strikingly similar to that of Case 1 in this report, even to the initial diagnosis of vitamin D resistant rickets and the later suspicion of renal tubular acidosis. They emphasize the importance of proper initial diagnosis in avoiding the potential hazards of vitamin D intoxication.

The second case, the father of Patient 1, indicates a familial incidence of this condition and suggests the benign nature of the affection. The third case is somewhat different from Case 1 and has certain features suggestive of chondrodysplasia in "extrametaphyseal" areas. The isolated metaphyseal lesion in this patient is, however, quite similar to and readily confused with active rickets.

SUMMARY

Three patients with bone lesions suggestive of rickets are described, in whom no abnormality of calcium and phosphorus metabolism was noted. This appears to be a

form of dyschondroplasia primarily involving metaphyseal bone and producing radiographic changes in the metaphysis resembling osteomalacia.

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Obstruction of the bladder neck in the male infant and child

Present concepts of diagnostic methods and management, and a report of 14 cases

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OBSTRUCTION of the bladder neck is a common cause of kidney destruction in male infants and children. Since this disease produces irreversible and progressive kidney damage which can be arrested only by relief of obstruction, early diagnosis and treatment are imperative. Conservatism in diagnostic methods and surgical treatment is as harmful as it would be in the management of Wilms' tumor.

PATHOLOGY AND AGE AT PATHOGENESIS

It has been well established[1, 2, 3] that renal secretion begins in the fetal period, and that high-grade obstruction of the bladder neck in the fetus can produce advanced hydronephrotic atrophy incompatible with extrauterine life. Indeed, the fetal hydronephrosis and bladder distention can be so tremendous that a parturition problem is created. On the other hand, the obstruction can be minimal and produce only trifling symptoms and barely discernible back pressure on the kidneys. In such cases, significant pathologic changes may not occur until the postpubertal period. Thus we have two extremes: the nonviable newborn infant with completely destroyed kidneys, and the young adult with borderline vesical neck contracture and equivocal symptoms. The vast majority of cases, however, lie between these two points, and occur in young children with kidney function good enough to sustain life, but obstruction severe enough to cause rapidly progressive renal destruction and failure. For these children, the only chance for survival lies in early diagnosis and treatment.

Types of bladder neck obstruction. It is commonly thought that nearly all cases of bladder neck obstruction in boys are produced by congenital valves of the prostatic urethra. These, however, represent a minority of the obstructing mechanisms[4] of which probably at least four exist (Fig. 1):

1. Congenital valves of the prostatic urethra. These were first described by Hugh

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Young[5] in 1919 and consist of mucosal folds in the prostatic urethra extending between the verumontanum and the lateral walls (Fig. 2*A*). They present no obstruction to the retrograde passage of a catheter, so this cannot be used as a diagnostic test. They may be difficult to identify cystoscopically because the influx of water through the instrument holds them open. On urination, however, they balloon out, causing obstruction which prevents the urine from flowing except under high pressure and only a few drops at a time. The musculature of the bladder becomes hypertrophied in order to force the urine past the obstruction. The hypertrophied detrusor muscle working against the vesical neck obstruction causes back pressure against the kidneys, with a resulting tremendous dilatation of the upper urinary tract. In turn the ureteral musculature becomes hypertrophied to aid the downward peristalsis.

2. Hypertrophy of the verumontanum. This may exist alone or in combination with congenital valves. It consists of an enlargement of the verumontanum to two to three times its normal size with resulting occlusion of the prostatic urethra. The effect of the obstruction on the bladder and the upper urinary tract is the same as that caused by congenital valves. Pathologic study of the verumontanum has shown no specific type of change (Fig. 2*B*).

3. Contracture of the vesical outlet. This is the most common form of bladder neck obstruction and also occurs in girls, although we have seen no cases of sufficient severity in female children to require operation during the last 10 years. It was first described in 1915.[6] Vesical neck contracture is characterized by an increase in the submucosal connective tissue,[7] which eventually involves the entire bladder neck in a collarlike manner. Microscopically there is fibrosis of the tissue of the bladder neck (Fig. 2*C*).

4. Hyperplasia of the prostate. This may or may not be associated with vesical neck contracture. Normal immature prostatic tissue forms an obstruction to the bladder outlet, resembling superficially the type of outlet seen in aging males. There are no distinct lobes seen. Instead the prostate forms a small mound of hyperplastic tissue on the floor of the bladder (Fig. 2*D*).

All four types of bladder neck obstruction produce identical changes in the upper urinary tract. The degree of obstruction, rather than the type of pathology is the sole determining factor in the amount of change produced in the bladder, ureters, and kidneys.

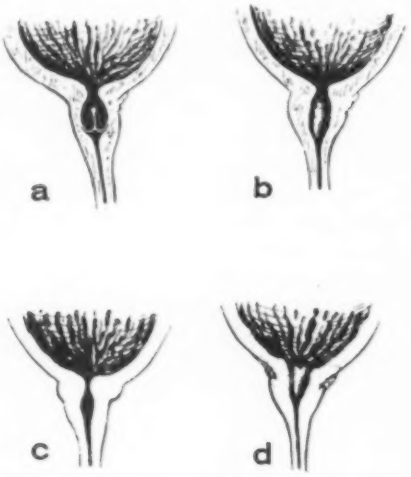


Fig. 1. Diagram illustrating the four types of vesical neck obstruction. *a*, Valves of the prostatic urethra. *b*, Hypertrophy of the verumontanum. *c*, Vesical neck contracture. *d*, Hyperplasia of the prostate.

SIGNS AND SYMPTOMS

Nesbit and Baum[8] have commented on the desirability of instructing parents in methods of checking on the urinary tracts of their newborn infants as well as on dietary and bowel habits. If mothers were equally well trained in the recognition of urinary obstruction as they are in the recognition of diarrhea, chronic urinary retention would not remain undetected for long periods of time. These symptoms may be divided into the early signs and symptoms of pure obstruction, and the later ones of infection, renal failure, and uremia.

A. Signs and symptoms of obstruction. Minor degrees of obstruction may cause only

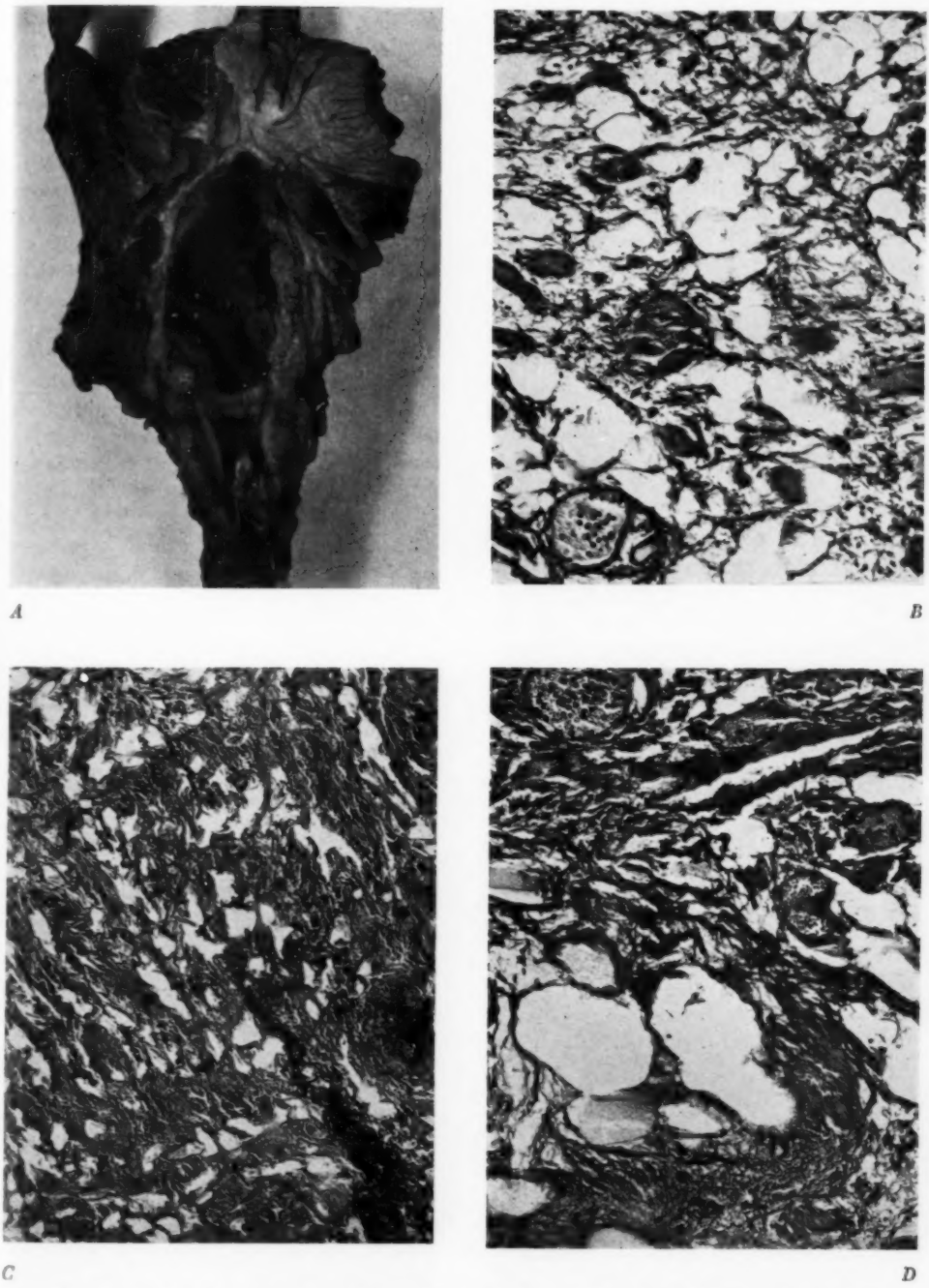


Fig. 2. *A*, Gross postmortem specimen of congenital prostatic valves. Note attachment to verumontanum and tremendous hypertrophy of the bladder musculature. *B*, Microscopic section of hypertrophied verumontanum. *C*, Same of vesical neck contracture. *D*, Hyperplasia of the prostate.

slight diminution in the force and size of the urinary stream, which is thin in caliber and lacks the proper projectile force when the baby is lying on his back. More pronounced obstruction produces clear-cut symptoms, consisting of a poor dribbling stream which runs out slowly, or only drop by drop. The infant may become purple in the face from straining, or cry while he voids. Because the bladder is never completely empty, the child spends a great deal of time trying to push out his urine, with resulting frequency of urination. Older children may even learn to push on the suprapubic area to assist urination. Because the clothing is wet due to overflow incontinence, a false diagnosis of enuresis may be made. This confusion may be avoided by recalling the axiom that while nocturnal wetting is usually functional, daytime wetting in older children is often caused by organic changes. Any increase in the intra-abdominal pressure caused by coughing, sneezing, crying, or sudden movements causes the expression of small amounts of urine by overflow. A child whose diaper is always wet should be suspected of having a constantly full bladder.

The bladder may be felt as a rounded mass in the suprapubic area. Pressure on it

A

B

C

Fig. 3. Cystograms illustrating various phases of bladder outlet obstruction. *A*, Dilated prostatic urethra associated with congenital prostatic valves or a hypertrophied verumontanum. *B*, Vesical neck contracture. *C*, Voiding cystogram in outlet obstruction, showing reflux up dilated ureters.

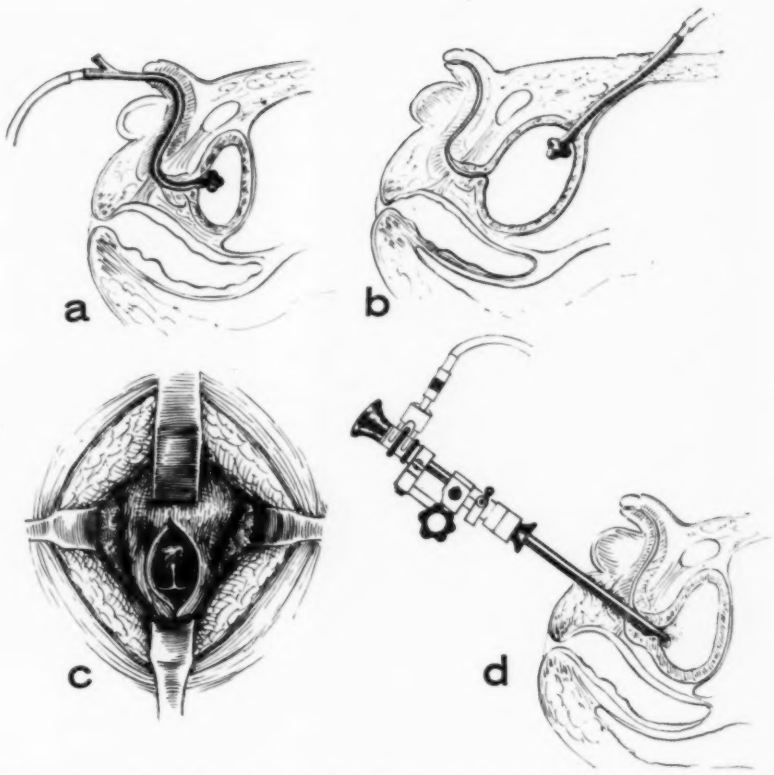


Fig. 4. Management of vesical neck obstruction. *Temporary treatment* consists of drainage to restore renal function and electrolyte balance. *a,* Urethral catheter drainage or *(b)* suprapubic drainage. The tube must be inserted through the dome of the bladder or contraction of the organ will result. A long sinus tract emerging high on the abdomen will prevent leakage. *Definitive treatment* is by *(c)* retropubic exposure of the bladder neck and prostate at which time the obstructing valves, prostate, or verumontanum may be removed, or a V-Y plastic operation performed on the bladder neck. The obstructing tissue, or scar, can also be removed transurethrally *(d).*

will produce a dribbling flow of urine from the urethra. If the obstruction has produced bilateral hydronephrosis, the kidneys may be palpated in the flanks.

B. Signs and symptoms of infection and of poor renal function. Persistent obstruction of the bladder neck invariably leads to infection, with an exacerbation of all symptoms of bladder irritability. Furthermore, the obstruction makes the resulting infection impervious to treatment by antibiotics. For this reason alone, all children with chronic or recurrent urinary tract infection should be suspected of having urinary obstruction until it is proved otherwise. Cystitis and renal infection with chills, fever, and prostration mark the superimposition of bacterial infection on the already damaged urinary tract. Infection leads to further failure of renal function, which produces symptoms ranging from failure to gain weight and "gastrointestinal upsets" to frank loss of weight, acidosis, convulsions, and coma.

Frequently infants are seen in whom the signs of renal failure occur before infection has appeared. Such children may be admitted

A

B

Fig. 5. Case 1, 7-year-old boy admitted with a distended bladder and overflow incontinence. *A*, Excretory urogram showing distended bladder with minimal hydroureters. Cystoscopy revealed a vesical neck contracture with hypertrophy of the verumontanum. *B*, Despite three transurethral resections, the hydronephrosis became worse. *C*, For this reason the patient was placed on semi-

to the hospital as presenting nutritional problems, with failure to gain weight or with actual loss of weight. Careful examination should reveal a distended bladder and a poor urinary stream, and a careful history will disclose voiding abnormalities.

It should be the rule of every newborn nursery to make sure that no baby is discharged from the hospital until he has been observed by qualified personnel to void a good strong stream. This would assure recognition of the baby with a potentially lethal urinary tract obstruction at the best possible time for its correction. Furthermore, every mother being instructed by the pediatrician in the care and feeding of her newborn infant should also be instructed in the observance of his voiding habits.

DIAGNOSIS

In most instances, this is simple and based on the following points:

A. Observation of the infant's voiding. This is an easy test to make and can be carried out in the office or at the patient's home. Voiding can usually be initiated by pouring warm water over the genitals of young children. An older child can, of course, void at will. A poor stream will be noted, as well as straining on the part of the child.

B. Intravenous urography. This provides an invaluable general urologic survey of the child without any risk of instrumentation. Although a few exceptions exist, significant urinary obstruction seldom occurs without evidence of nonvisualization or of dilatation of the urinary tract. The latter may show

C

D

permanent suprapubic drainage, which resulted in normal pyelograms. He stayed on suprapubic drainage until the age of 16 during which time he led a normal life in grade and high school. At that time, transurethral resection of the remaining obstruction was carried out with an adult resectoscope. *D*, The patient now voids normally without residuum, has sterile urine, and normal pyelograms and has enlisted in the Navy.

tremendous dilatation of the bladder, ureters, and/or kidneys. Failure to excrete the contrast medium is in itself highly suggestive of urinary tract obstruction. In addition, residual urine may be determined by taking a final film immediately after the patient voids. This will reveal the presence or absence of residual urine and should always be a part of the routine intravenous urography of children.

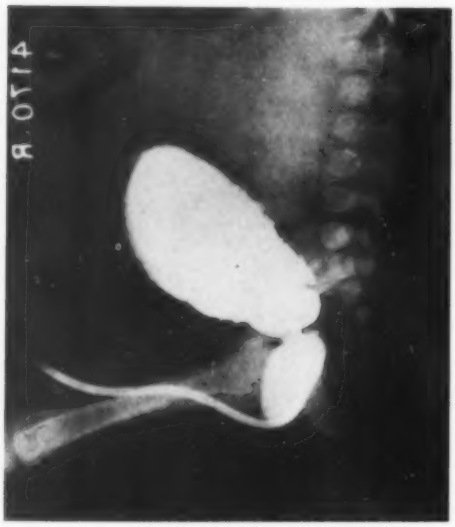
C. The determination of residual urine. This is the most significant diagnostic feature of vesical neck obstruction. It is determined by catheterization immediately after the child has voided. The reluctance to catheterize the patient, due to fear of infection, has no place in the management of children with overt or suspected bladder neck obstruction. Infinitely more risk is taken by failure to diagnose the condition than by the slight possibility of postcatheterization infection. The latter rarely occurs when catheterization is carried out gently, aseptically, and by experienced personnel. If infection should result in a patient with a normal urinary tract, it may be quickly eliminated with antibiotics; if it occurs in a patient with a large amount of residual urine and dilatation of the upper urinary tract, the child requires catheter drainage as treatment. Failure to catheterize these patients is not defensible.

Catheterization should be done gently, under strictly aseptic precautions, and in the hospital where cystograms may be obtained at the time the catheter is passed. Failure to

carry out cystography at the time of catheterization is neglect on the part of the diagnostician, as it will require another catheterization at a later date.

D. Cystography. As stated above, this is carried out following catheterization for residual urine. A suggested routine is as follows:

1. Have the child void, or wait until he voids, if he is too young to void voluntarily. Immediately catheterize him with a small soft rubber catheter under strictly aseptic condi-



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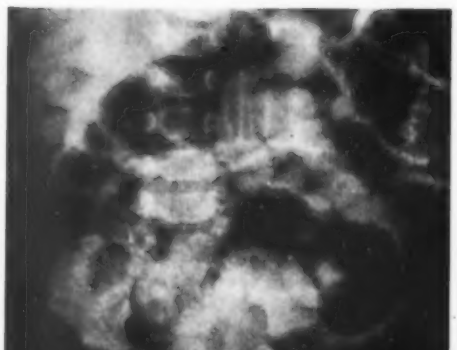

B

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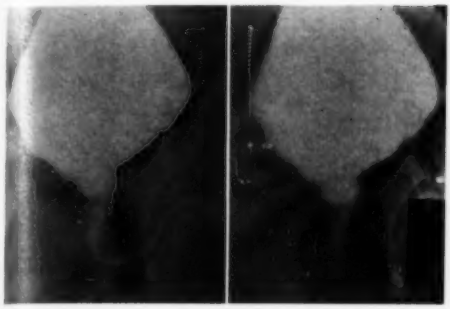
Fig. 6. Case 2, 6-week-old baby admitted with weight loss, convulsions, and a suprapubic mass. The urine was filled with pus cells and the blood urea nitrogen was 56 mg. per cent. *A*, Cystogram on admission showing dilated prostatic urethra suggestive of prostatic valves or of enlarged verumontanum. The patient was placed on suprapubic drainage because of his poor condition; there was a fall in the urea nitrogen, and excretory urography was performed demonstrating bilateral severe hydroureters and hydronephrosis *(B)*. Maintenance of suprapubic drainage for 3 months resulted in marked improvement of the hydronephroses *(C)*. The boy was left on suprapubic drainage until the age of 8, when a transurethral resection of a hypertrophied verumontanum was performed. This resulted in an improvement in the vesical outlet contour *(D)*, disappearance of the residual urine, and greatly improved pyelograms *(E)*.



D

E

tions, using plenty of sterile lubricant. The easy passage of the catheter does not rule out vesical neck obstruction, as obstruction exists only to antegrade flow of urine from the bladder, not to retrograde catheterization. The amount of urine left in the bladder is measured.

2. Tape the catheter to the penis, or if it is a Foley catheter, it may be inflated. The bladder is filled with a radiopaque solution. It is best to use some nonirritating solution, such as 15 per cent Skiodan, which has been warmed to body temperature. The exact amount to be injected depends on the size of the child, and may vary from 50 c.c. in an infant to 250 c.c. in an 8- or 9-year-old boy. If the bladder is filled by gravity, with a syringe held 1 foot above the level of the symphysis and the contrast medium allowed to run in until it stops, overfilling cannot occur.

3. After filling, the catheter is clamped and anteroposterior and lateral films are exposed to determine the relative size of the bladder and the presence or absence of trabeculation and possible reflux.

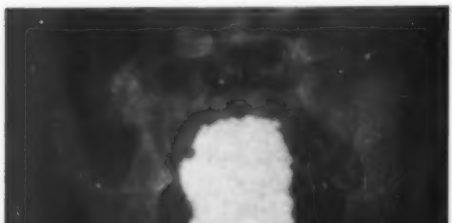
4. Another film is taken 10 minutes later to note the presence or absence of reflux up the ureters (delayed cystogram).

5. The catheter is removed and the patient instructed to void. Two exposures are made during the act of voiding. One is an oblique film to outline the prostatic urethra. This may reveal a dilated urethra suggestive of urethral valves or an enlarged verumontanum (Fig. 3*A*), or a vesical neck contracture without dilatation of the prostatic urethra (Fig. 3*B*). A second film of the abdomen is made to observe the presence or absence of urethral reflux which may occur only during the act of voiding (Fig. 3*C*). The value of delayed and voiding cystograms to demonstrate reflux is well established.[9, 10]

If the patient is too young to cooperate, the penis may be compressed gently between gauze after the catheter is withdrawn. The patient is placed in an oblique position and the pressure on the penis is released. Usually the infant will void immediately to get rid of the solution. If not, pinching of the skin of the abdomen may initiate micturition, or warm water can be poured over the genitals.

Ureteral reflux is of paramount importance in diagnosing vesical neck obstruction. Prolonged outlet obstruction will produce reflux[11] which may reach the point where these patients literally void up their ureters. This in turn may make the diagnosis of residual urine impossible except by the demonstration of ureteral regurgitation and its extent.

Although it is conceivable that ureteral reflux may occasionally occur in normal children,[12] the frequent association of ure-



A

B

C

D

Fig. 7. Case 3, 5-month-old boy admitted with a suprapubic mass and overflow dribbling. The blood urea nitrogen was not elevated. *A* and *B*, Anterior and lateral cystograms showing a dilated prostatic urethra and trabeculation of the bladder. *C*, Excretory urogram demonstrating severe hydronephroses and hydroureters. The patient was placed on catheter drainage until optimal renal function was obtained. Cystoscopy at that time showed hyperplasia of the prostate. Transurethral resection was carried out through a perineal urethrotomy at the same time, because of the small caliber of the penile urethra. *D*, Two years later the patient was voiding without residual urine or infection. The pyelograms are greatly improved.

terovesical reflux with vesical neck obstruction and other abnormalities has been felt by many[11, 13] to indicate that this reflux means that the urine is being forced up the ureters because it cannot pass out through the urethra. It would certainly appear that the

demonstration of ureteral reflux makes it mandatory to carry out studies for the presence of bladder neck obstruction.

The megacystitis syndrome. Although not within the scope of this paper, this complicated condition, of uncertain etiology, may require differentiation from pure bladder neck obstruction. As described by Williams the urinary abnormalities consist of a large thin bladder with dilated ureters and bilateral ureteral reflux. Cystoscopy reveals a large trigone with widely separated ureteral orifices, which are dilated. Here, cytography is of prime importance in demonstrating the changes, which may be missed by excretory urography. The interested reader is referred to the recent work by Paquin and his group.[16]

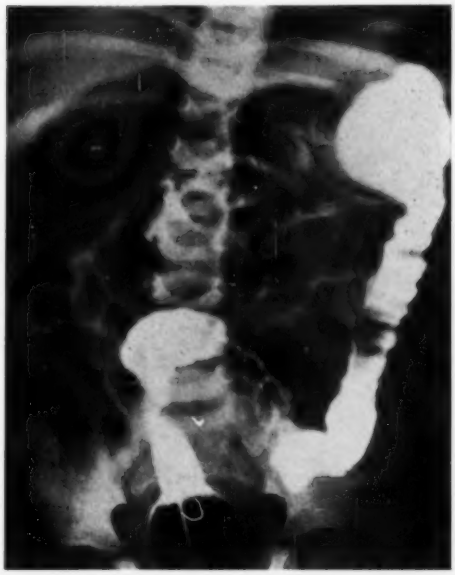
TREATMENT

Treatment may be divided into (1) preliminary lifesaving measures and (2) definitive surgery designed to overcome the obstruction.

1. Preliminary treatment. This is necessary in patients with bladder neck obstruction who have dilated, infected urinary tracts and renal failure, as evidenced by elevation of the blood urea nitrogen. The simplest initial treatment is the insertion of an indwelling Foley catheter (Fig. 4*A*). This is followed by as long a period of drainage as is necessary to restore the damaged urinary tract to its optimum efficiency. On such therapy, there is a regression of the hydronephrosis, subsidence of infection, and return of renal function, as evidenced by progressive lowering of the blood urea nitrogen.

Certain children will not tolerate prolonged catheter drainage. Owing to the small caliber of the urethral catheter, incrustations occur within the catheter and result in secondary cystitis and urethritis. The catheter may become blocked and require frequent changing and almost constant irrigations. Furthermore, the pressure on the trigone may produce vesical spasm with resultant pain and occlusion of the ureteral orifices.

In children who cannot tolerate indwelling catheter drainage, suprapubic cystotomy is recommended. Such drainage, to be efficient, should be carried out so that the Pezzer catheter is introduced through the dome of the bladder where it will not press down on the trigone and cause vesical spasm with secondary ureteral obstruction. Furthermore, a long sinus tract between the bladder and the skin is desirable to prevent leakage around the tube. This may be effected by bringing the tube out from the abdomen near the umbilicus (Fig. 4*B*) through a stab wound in the rectus sheath and through the skin. Children with this type of drainage do very well, do not have bladder spasm, and stay dry. We have had one such child on suprapubic drainage for over 11 years. He went through high school and engaged in the usual activities with the rest of his classmates. The tube was opened at periodic intervals during the day as would be necessary for normal voiding.



A

Fig. 8. Case 4, 18-month-old boy with chief complaint of repeated episodes of fever, vomiting, and abdominal distention. *A*, Barium enema revealed apparent obstruction at the splenic flexure. At laparotomy a dilated bladder and left ureter were found. Subsequent studies revealed a urea nitrogen of 25 mg. per cent and residual urine of 250 c.c.

B

D

C

E

Fig. 8. *B* and *C*, Cystogram in anterior and oblique projection revealed bilateral reflux up greatly dilated ureters to hydronephrotic kidneys. The patient was kept on catheter drainage until the urea nitrogen became normal, when a transurethral resection of a vesical neck contracture was performed. This did not relieve him of residual urine, nor did a subsequent transurethral procedure. *D*, Marked hydronephrosis persisted. Accordingly he was put on semipermanent suprapubic drainage to preserve renal function. He is now 10 years old, and the vesical obstruction will be resected with the adult resectoscope when he is large enough. *E*, Recent pyelograms show improved renal function with persistent hydronephrosis.

A

B

C

Fig. 9. Case 5, 6-month-old boy admitted with weight loss, vomiting, and cachexia. There were a large suprapubic mass and 200 c.c. of residual urine. The blood urea nitrogen was 57 mg. per cent. *A*, A cystogram revealed a trabeculated bladder and reflux up a dilated left ureter to a hydronephrotic kidney. Because of sepsis and the patient's poor condition, suprapubic drainage was instituted. *B*, Three months later a right pyonephrosis developed requiring drainage by nephrostomy. The patient lived for 2 years on combined drainage, having severe intermittent attacks of sepsis; he died of renal failure and sepsis. *C*, Autopsy specimen of urinary tract showing prostatic valves, hypertrophied bladder, and kidneys damaged by infection and back pressure. This urinary tract was too badly damaged to be saved when the patient was first seen.

A

C

B

Fig. 10. Case 6, 12-year-old boy admitted because of protuberant abdomen and urinary frequency. The urine was filled with pus and bacilli. Examination showed the bladder to be filled to the umbilicus; the blood urea nitrogen was 29 mg. per cent. *A*, Cystogram showing reflux up tremendously dilated right ureter to huge hydronephrosis. The patient was placed on suprapubic drainage and has remained on it since (6 years). Two weeks after drainage, function had improved so that intravenous urography was possible. *B*, This revealed a diminution of the right hydronephrosis. *C*, At that time the left kidney was also delineated by reflux. The patient has continued to live precariously, with recurrent bouts of sepsis and uremia. No definitive surgery has been attempted because of his poor condition.

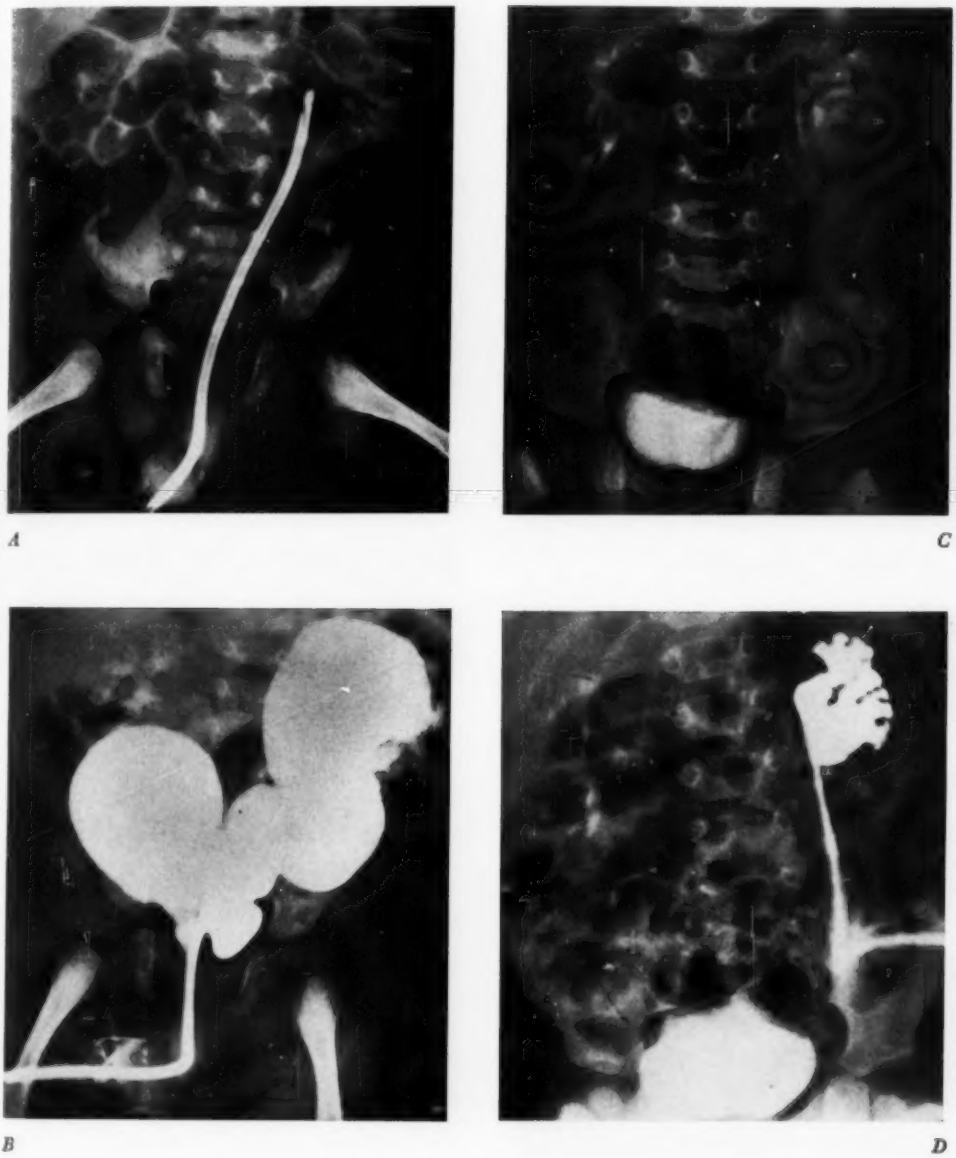


Fig. 11. Case 7. An unusual type of bladder outlet obstruction caused by a left ectopic ureter opening into the prostatic urethra. The patient, a 5-week-old boy, was admitted with a distended bladder and overflow incontinence. *A*, Urethral catheter passes up ectopic ureter instead of into bladder. *B*, Contrast medium demonstrates an ectopic hydroureter occluding the vesical outlet, with distended bladder and minimal right hydronephrosis. Cystoscopy confirmed the impression of ectopic ureter. The latter was resected and the left kidney drained by cutaneous ureterostomy to the left lower quadrant. *C*, There was apparent return of function of the left kidney following ureterostomy but it lasted only 6 months. *D*, Retrograde injection of left ureter shows only a hydronephrotic shell remaining; nephrectomy and ureterectomy were performed. The patient is living and well with normal bladder function.

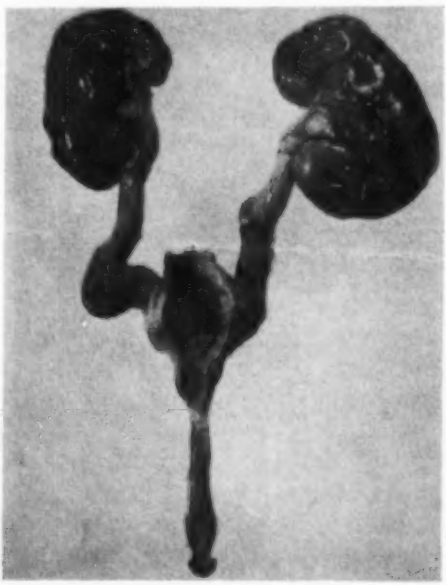
Patients who require constant drainage, as a result of severe hydronephrosis, must drain these tubes continuously into plastic leg urinals to prevent back pressure on the kidneys. These leg bags are clean, odorless, disposable, and relatively inexpensive.

2. Definitive treatment. It is now well established that there are two ways in which definitive removal of the obstruction at the bladder neck can be carried out. These include (1) retropubic exposure of the prostate with excision of the valves or obstructing tissue and (2) transurethral resection. Suprapubic transvesical excision has become unpopular because of the extremely poor results and inadequate visualization.[14]

a. Retropubic plastic procedures. These were devised by Lich[15] and others[4, 11] and have been the most effective method of dealing with all types of obstruction at the bladder neck (Fig. 3*C*). The prostate is exposed retropubically under direct vision, the bladder is opened anteriorly in a longitudinal direction, and the obstructing valves or tissue are removed. A wedge may be taken out of the vesical neck if a contracture is present. Following this the bladder is closed in such a manner as to increase the diameter of the vesical outlet (transversely or by Y-V closure).

b. Transurethral resection. This method is most effective in older children rather than in tiny infants. In children under 1 or 2 years of age it is impossible to introduce the infant resectoscope into the bladder for this procedure without a perineal urethrostomy. This is a valuable adjunct in the treatment of vesical neck obstruction in children and is imperative unless the child is 3 or 4 years old or older. The insertion of the resectoscope

A



B

Fig. 12. Case 8, 3-year-old boy admitted with convulsions and a blood pressure of 180/120. There had been dribbling overflow incontinence since birth. Blood urea nitrogen was 29 mg. per cent. Catheterization revealed 560 c.c. of residual urine. *A*, The cystogram showed marked trabeculation without reflux. The patient was placed on suprapubic drainage but died of renal failure after 2 months. *B*, Autopsy specimen showing urethral valves and dilatation of the upper urinary tract with multiple abscesses.

through the perineal urethra obviates the complications of urethral stricture, which will inevitably occur when a rigid instrument is inserted into a small urethra. In older children, the infant resectoscope is easily passed through the entire urethra and visualization is simple.

Cystoscopic evaluation of the bladder outlet in children is difficult, because of the small lens system in infant resectoscopes and the indefinite landmarks in the urethras of small boys. In general the operator should assume that if the child does not empty his bladder and trabeculation exists in the bladder, there is high-grade obstruction at the bladder neck, whether or not this can be definitely distinguished with the lens. Resection should then be boldly undertaken on the bladder neck, staying away from the external sphincter, which lies distal to the verumontanum. If a large verumontanum or valves are present, these too should be resected. The operator should remember that in children the ureteral orifices are very close to the vesical neck and must be avoided during the resection.

We have found that one or more transurethral resections have been necessary in some of our patients to enable them to void without residual urine and to eliminate the infection. In one instance, the patient after three resections was still not urinating properly and carried residual urine. Accordingly permanent suprapubic drainage was established. When he reached the age of 16, an adult resectoscope was introduced and the vesical neck contracture easily resected. He now has a perfectly adequate urinary tract. Semipermanent suprapubic drainage is recommended for all boys in whom unequivocal relief of obstruction is not obtained. It preserves renal function in the growing boy until he is large enough to permit transurethral surgery.

There is no particular advantage in the transurethral route over the retropubic one. We have favored the former because we feel a better ultimate visualization of the outlet is to be had during transurethral surgery and because it carriers almost a negligible mor-

A

B

Fig. 13. Case 9, 27-month-old boy admitted because of nausea and vomiting, weight loss, and a suprapubic mass. Urine contained pus and albumin. The urea nitrogen was normal. *A,* Intravenous urogram at admission showed bilateral hydronephrosis. *B,* The cystogram revealed a trabeculated bladder without reflux. Cystoscopy revealed hypertrophy of the verumontanum and prostate. After preliminary catheter drainage, transurethral resection was performed twice, resulting in the ablation of residual urine and the appearance of a good urinary stream. This patient did not return to the hospital for pyelograms and could not be traced.

A

B

Fig. 14. Case 10, 10-year-old boy admitted with a distended bladder and overflow incontinence, which had been present all his life. The blood urea nitrogen was normal. *A*, Intravenous urogram following catheter drainage shows a normal right kidney and no function on the left side. Cystoscopy revealed hypertrophy of all three lobes of the prostate, and transurethral resection was carried out. Following resection there was no longer any residual urine, and the urinary stream became adequate.
B, Intravenous urogram 1 year following operation shows return of function to the left kidney, although minimal hydronephrosis persists.

bidity and mortality. Equally good results have been obtained by others with retropubic methods. We have found this exposure difficult in older children.

CASE REPORTS

The cases depicted in Figs. 5 to 17 represent 13 of 16 cases of vesical neck obstruction seen at St. Christopher's Hospital for Children between 1949 and 1959. Three cases have been excluded because of inadequate follow-up studies. The unconventional style of presentation consisting of selected urograms with an abbreviated legend summarizing the history is felt to be more instructive than the usual detailed protocols.*

15A

*We wish to express our appreciation to Dr. James Arey, Pathologist, St. Christopher's Hospital for Children, who reviewed all pathologic sections in these cases.

Fig. 15. Case 11, 4-year-old boy admitted to the hospital for tonsillectomy with no history of urinary difficulties. Preoperative urinalysis revealed innumerable pus cells. *A,* Excretory urogram showing severe left hydronephrosis and hydroureter, apparently caused by ureterovesical obstruction. There is also apparent absence of the right kidney. *B,* Cystogram following voiding reveals absence of reflux and a small amount (25 c.c.) of residual urine. The patient voided with a fair stream and had no incontinence. Cystoscopy revealed an apparently normal outlet and no bladder trabeculation. There was only a nonpatent dimple in the region of the right ureteral orifice. *C,* A diagnosis of left ureterovesical obstruction was made, and the ureter was reimplanted into the bladder through a submucosal tunnel. The patient was left on suprapubic drainage. *D,* This resulted in improvement in function of *both* kidneys with the excretion of contrast medium from the supposedly absent right kidney.

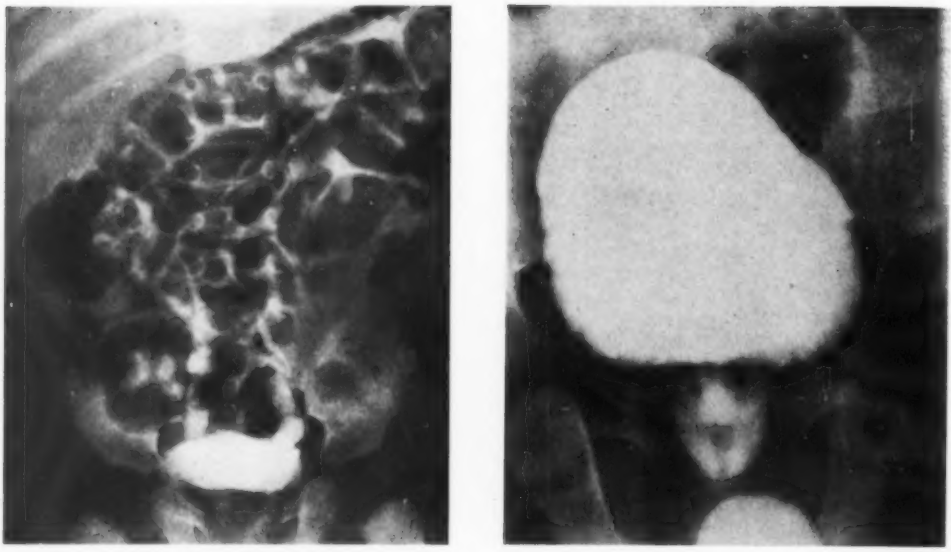
Since suprapubic drainage had produced this effect, it was realized that an undiagnosed obstruction of the vesical neck was present, and transurethral resection was carried out 2 months later. This resulted in the elimination of the small amount of residual urine and the maintenance of function in the right kidney.

Vesical neck contracture in children should be suspected whenever there is residual urine and dilatation of the upper tract, or ureteral reflux, despite the apparent normal cystoscopic appearance of the outlet.

C

B

D



A *B*

Fig. 16. Case 12, 3-month-old boy admitted because of failure to gain weight. The blood urea nitrogen was 21 mg. per cent, and there was 30 c.c. of residual urine. *A*, Excretory urogram showed bilateral ureterectasia with little hydronephrosis. *B*, Cystogram showed dilatation of the prostatic urethra, without reflux up the ureters. The baby was too small to be treated with the infant resectoscope, and the changes were too borderline to require catheter or supropubic drainage, so he has been followed for a year. Excretory urograms at 15 months showed no increase in the ureteral dilatation and a normal blood urea nitrogen. The amount of residual urine has remained the same. Cystoscopy has shown obstructing prostatic tissue. The vesical obstruction will be resected when he is large enough to permit the use of the infant resectoscope.

Fig. 17. Case 13, 3-month-old boy admitted with weight loss and a blood urea nitrogen of 100 mg. per cent. The bladder was distended. The cystogram shows bilateral reflux up the ureters. Despite catheter drainage and fluid therapy, the baby died soon after these studies were made. Autopsy revealed a vesical neck contracture.

SUMMARY

1. Unrecognized vesical neck obstruction is a frequent cause of renal destruction in male infants and children.

2. This condition should be diagnosed in the postnatal period in the newborn nursery. No newborn infant should be discharged from the hospital until he has been observed to void with a good stream.

3. Temporary treatment consists of catheter or suprapubic drainage. The latter can be continued indefinitely if kidney function is poor.

4. Definitive treatment is by retropubic or transurethral surgery. If not completely successful, suprapubic drainage should be instituted as a kidney-saving measure until the patient is old enough to permit an adequate operative procedure.

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Human albumin in exchange transfusion

A quantitative study of the influence of added human albumin on bilirubin removal

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THE value of exchange transfusion in the initial treatment of infants with erythroblastosis fetalis is firmly established,[2] but the management by repeated exchange transfusions in babies with a secondary hyperbilirubinemia is far from satisfactory. Each transfusion produces biochemical changes,[6] sudden death can always supervene, and much time of skilled workers is expended. An orthodox exchange transfusion readily removes sensitized erythrocytes, but large amounts of bilirubin remain in the infant because of its distribution in plasma, tissue fluid, and cells.[9]

Any method of increasing bilirubin removal or reducing the need for re-exchange demands serious and urgent consideration.

Brown, Zuelzer, and Robinson[3] clearly indicated that bilirubin rapidly diffused into the circulation during exchange transfusion. Improved bilirubin exchange could be achieved by the introduction of a bilirubin binding substance into the blood stream prior to exchange. This would favor diffusion into the blood and a more adequate removal of bilirubin by the orthodox exchange technique. Recently Odell[11, 12] has demonstrated the elevation of serum bilirubin in the human infant following intravenous administration of albumin.

Johnson and colleagues[5] working with icteric newborn rats demonstrated the protective value of intraperitoneal albumin in the prevention of kernicterus; Bowen, Porter, and Waters[1] using newborn puppies as experimental animals demonstrated that the neurotoxic effect of intravenous bilirubin was substantially mitigated by the concurrent injection of human albumin.

An investigation was therefore planned to ascertain whether human albumin would appreciably increase this diffusion process. Alternate babies were designated as controls or treated with salt-poor concentrated human albumin (25 Gm. albumin in 100 ml. of fluid) in the early stage of the exchange transfusion.

In each group the removed bilirubin was estimated quantitatively. This involved an initial introduction of Evans blue for blood volume determination, sampling the infant's

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blood before and after the exchange, and sampling the discarded or "waste blood."

MATERIAL

At the Royal Women's Hospital, Melbourne, all infants affected with erythroblastosis due to the Rh factor were treated in one unit, and these babies provided the clinical material for the trial.

The series included both premature and term babies. Controls and albumin-treated babies were selected alternately, and neither group contained a disproportionate number of small infants.

METHOD

The exchange transfusion was carried out by an experienced registrar, and one of the authors (W. H. K.) acted as monitor on every occasion. Increments of 10 ml. of Rh-negative, group specific, fresh citrated blood were introduced by a polyvinyl catheter in the umbilical vein. A transfusion rate of 16 ml. of blood per minute and a volume of 220 ml. of blood per kilogram of body weight were arbitrarily selected. Silicone coating of the exchange equipment and a very short waste delivery tube largely eliminated clotting problems. In some cases hemolysis of the discarded blood presented a difficulty for which no adequate solution was found.

Quantitative estimations were attempted on 32 infants but complete data were obtained for only 20 of them.

Exclusion of cases. Twelve infants were excluded on one or more of the following grounds (see Table III): (1) clotting of specimens of blood, 2 cases; (2) gross hemolysis of "waste blood," 1 case; (3) disagreement between the blood volume as determined by the independent methods of Evans blue dilution and fetal hemoglobin levels; (4) inadequate volume of exchange.

It is to be noted that no case was eliminated because it failed to support the thesis.

Procedure. 1. Immediately after insertion of the umbilical catheter, 5 ml. of blood was taken in a dry syringe as a blank for Evans blue determinations.

2. From a single syringe used in all patients, a known dose of 2.06 mg. of Evans blue was injected into the catheter, and the syringe and tubing were rinsed 3 times with the infant's blood.

3. After 5 minutes (to allow adequate mixing of the blood and dye), two 5 ml. samples were collected in heparinized tubes for estimations of levels of Evans blue, total bilirubin, fetal hemoglobin, and the hematocrit value.

4. Exchange transfusion was then carried out in the routine fashion in the control series.

In the group treated with albumin 12.5 Gm. of salt-poor concentrated human albumin was used at the beginning of the exchange, and a further 12.5 Gm. was introduced when the exchange was half completed. In the control group 220 ml. of blood per kilogram of body weight was exchanged, while in the albumin-treated series the total volume of fluid (albumin plus blood) was also 220 ml. The technique of albumin introduction was simple. Connection from the drip chamber of the blood transfusion set was made to the albumin solution and donor blood so that occlusion of the appropriate tube allowed the operator to choose one or the other as the exchange medium.

5. The last 10 ml. of blood withdrawn from the infant was collected in 2 heparinized tubes.

6. All the waste blood was meticulously delivered into a flask containing 50 mg. of heparin. Care was taken to agitate this waste gently but frequently during the exchange.

After inspection and measurement of the volume of the waste it was thoroughly mixed, and samples were taken for the various estimations.

Care was taken to carry out a balanced exchange. Special attention was paid to the rate of exchange and it will be noted that all infants in the albumin-treated series had a rather rapid exchange. In the control series the exchange rate was slower than intended in some patients, but this favored increased bilirubin excretion in the control group and does not vitiate the conclusion to be made later.

Evans blue (T-1824) concentration was estimated by the method of Tornberg.[17] Because this dye was compared in plasma of widely varying levels of jaundice, the accuracy of the method might be questioned. However, serial dilution of deeply icteric plasma with normal plasma to which was then added a constant amount of T-1824 showed no interference with bilirubin concentrations up to the maximum level of 20 mg. per cent present in the series.

Biochemical estimations. As large volumes of blood were available for testing, biochemical estimations were made under the most favorable conditions.

1. Hematocrit values were determined after spinning for 55 minutes at 3,000 r.p.m. in a radius of 14 cm.

2. Fetal hemoglobin was estimated by a modification of the Singer alkali denaturation technique.[14] Heparinized blood was centrifuged for 10 minutes at 3,000 r.p.m. The supernatant fluid was removed with the use of the Pasteur pipette for estimation of bilirubin. The red blood cells were washed with a large volume of isotonic saline solution and again centrifuged for 10 minutes at 3,000 r.p.m.

One milliliter of packed cells was added to 1.5 ml. of distilled water and a trace of saponin powder was blown in by Pasteur pipette. The mixture was thoroughly shaken and after 10 minutes the alkali denaturation technique of Singer was applied to the laked blood. In many specimens it had been found that Singer's method of adding toluene to the cells and water and then centrifuging to separate the layers was unsatisfactory. It was sometimes impossible to separate the lower red layer cleanly from the upper 2 layers. With the saponin method it was found necessary to allow 2 minutes before addition of ammonium sulfate to precipitate the denatured adult hemoglobin. Excellent duplicates were obtained with this modification.

3. Bilirubin was estimated by Powell's method[13] with use of Ehrlich's diazo mixture with sodium benzoate urea as a coupling agent. In a separate series of experiments it was shown that Evans blue in concentrations up to 2 per cent did not interfere appreciably with estimation of the bilirubin.

Percentage exchanges of fetal red blood cells, plasma, and bilirubin.

1. *Fetal red blood cell exchange.* The fetal red cell exchange was calculated from the following formula:

$$\frac{\text{(initial – final) concentration of circulating fetal hemoglobin}}{\text{initial concentration of circulating fetal hemoglobin}} \times 100\%$$

2. *Plasma exchange.* The plasma exchange was calculated from the concentration of Evans blue in the final sample withdrawn from the baby during the transfusion. It was assumed that the total blood volume remained unaltered throughout the exchange since in our patients this was undertaken at least 6 hours after birth when the plasma shift was judged to be complete,[7, 16] and a balanced exchange was always carried out.

Circulating Evans blue at end of transfusion =

$$\text{blood volume} \times \frac{100 \text{ (hematocrit} \times 0.83)}{100} \times \text{final concentration of Evans blue (mg.)}$$

Plasma exchange =

$$\frac{\text{2.06 – Evans blue remaining in circulation}}{\text{2.06}} \times 100\%$$

(2.06 mg. of Evans blue initially injected)

(A) Evans blue method using the corrections for trapped plasma and body venous hematocrit advocated by Chaplin, Mollison, and Vetter.[4, 5]

Blood volume (ml.) =

$$\frac{\text{initial dose of Evans blue (mg.)}}{\text{plasma concentration of Evans blue (mg. \%)}} \times \frac{100}{100 \text{ (hematocrit} \times 0.83)}$$

(B) Brown, Zuelzer, and Robinson's fetal hemoglobin method.[3] Fetal hemoglobin initially circulating = fetal hemoglobin removed plus fetal hemoglobin circulating after exchange.

Blood volume × initial fetal hemoglobin = (volume blood exchanged × fetal hemoglobin in waste) + (blood volume × final fetal hemoglobin).

Therefore, blood volume (ml.) =

$$\frac{\text{fetal hemoglobin concentration in waste} \times \text{volume waste}}{\text{(initial} - \text{final) concentrations of fetal hemoglobin in blood}}$$

3. *Bilirubin exchange.* The bilirubin exchange was calculated from the formula:

$$\frac{\text{mg. of bilirubin recovered from waste}}{\text{mg. of bilirubin circulating initially}} \times 100\%$$

The total amount of bilirubin circulating initially was calculated from the concentration of bilirubin in milligrams per cent in the specimen removed before any donor blood was given in the plasma volume at that time, determined by the Evans blue dilution technique.

The total quantity of bilirubin removed was estimated from its concentration in milligrams in the plasma fraction of the waste blood. The latter was calculated from the volume of waste blood and its hematocrit, corrected for trapped plasma.[5]

4. *Diffusion of bilirubin during exchange transfusion.* Since the percentage exchange of bilirubin was strictly analogous to that for plasma and fetal red blood cells, the bilirubin diffusion into the circulation during an exchange transfusion was indicated by the difference between the percentage bilirubin exchange and the percentage plasma exchange.

RESULTS

In Tables I and II all relevant biochemical data are presented.

The fetal hemoglobin estimations proved an excellent indicator for the percentage red blood cell exchange and for blood volume in the first transfusion. In subsequent exchanges the amount of fetal hemoglobin was so small that accurate estimation of the percentage red blood cell exchange and blood volume was difficult.

Both direct- and indirect-reacting bilirubin concentrations were determined on all specimens in the series. The direct-reacting fraction was so small in every case that only the total bilirubin figure has been quoted in the tables. As would be expected from theoretic considerations the percentage bilirubin exchange was always higher than the fetal red blood cell exchange.

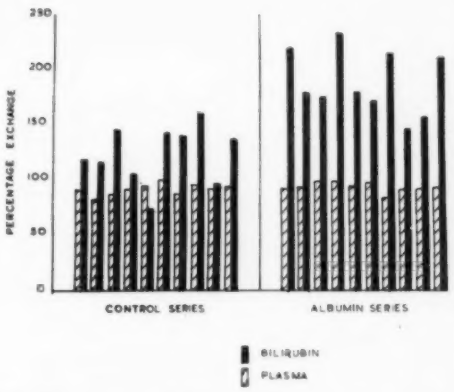

Fig. 1. Plasma and bilirubin exchange in control and treated infants.

Fig. 1 shows the percentage exchange of plasma (cross hatched) and bilirubin (solid column), each pair of columns representing a single baby. There is a striking improvement in bilirubin exchange in the albumin-treated series, with comparable plasma exchange in the twin groups.

Control group:
Mean exchange of plasma 91.4 per cent
Mean exchange of bilirubin 124 per cent
Albumin-treated group:
Mean exchange of plasma 92.7 per cent
Mean exchange of bilirubin 187 per cent

The difference between the mean percentage exchange in the plasma gave a nonsignificant value for t. In the bilirubin percentage exchange, the value of t was 3.68, based on 20 degrees of freedom and this exceeds the 1 per cent significance level.

The percentage plasma exchange, calculated by the Evans blue method, was undoubtedly a little high. It is known that Evans blue slowly disappears from the circulation but in the time of an average exchange this loss of dye would not invalidate

Table I. Biochemical findings in control and treated cases

Case	Dose of albumin (Gm.)	Dose of Evans blue (mg.)	Fetal hemoglobin levels (Gm./100 ml. blood)			Evans blue levels (mg./100 ml. plasma)		Bilirubin levels (mg./100 ml. plasma)		Hematocrit (uncorrected)		
			Initial	Final	Waste	Initial	Final	Initial	Waste	Initial (%)	Final (%)	Waste (%)
1	Nil	1.00	10.36	0.72	3.15	1.40	0.08	15.80	8.00	54	37	44
2	Nil	2.06	5.73	0.70	1.80	1.29	0.23	9.20	5.70	33	40	39
3	Nil	2.06	1.49	0.10	0.30	1.49	0.20	21.80	9.70	38	37	35
4	Nil	2.06	Too small to estimate			1.35	0.12	28.80	13.60	34.5	37	38.5
5	Nil	2.06	6.99	0.99	2.60	1.36	0.09	28.40	11.90	30	34	36
6	Nil	2.06	Too small to estimate			1.10	Nil	27.60	15.10	36	34	34
7	Nil	2.06	9.20	1.10	3.20	1.08	0.14	7.95	4.85	43	40	37
8	Nil	2.06	8.28	0.47	2.26	1.67	0.09	7.40	3.80	50	50	44
9	Nil	2.06	Too small to estimate			1.31	0.12	28.80	13.60	34.5	37	38.5
10	Nil	2.06	Too small to estimate			1.05	0.06	16.80	9.60	35	37	36
11	10	2.06	9.20	0.80	3.10	1.52	0.11	6.00	3.60	43	33.5	32
12	25	2.06	Too small to estimate			1.43	0.10	15.80	7.85	40	32	30
13	12.5	2.06	7.80	0.50	1.60	1.67	0.03	7.60	3.80	35	33	30
14	25	2.06	0.90	Too small to estimate		1.67	0.03	8.70	5.50	39	38	39
15	25	2.06	7.66	0.70	2.25	1.05	0.05	21.10	12.20	43	36	35
16	25	2.06	1.80	0.20	0.45	2.10	0.04	16.90	10.00	35	30	33
17	25	2.06	7.96	0.62	1.71	1.52	0.25	9.50	4.95	42	35	33
18	22.5	2.06	10.05	0.82	3.17	1.73	0.13	6.60	3.00	42	31	33
19	25	2.06	8.10	0.90	2.10	1.22	0.13	10.35	5.15	44	37	36
20	25	2.06	12.70	1.30	3.40	2.24	0.13	4.45	2.60	56	35	38

Table II. Blood volume and details of exchange in control and treated cases

Case	Birth weight (Gm.)	Albumin	Volume exchange (ml.)	Ratio (volume exchange to body weight)	Plasma volume (ml.)	Blood volume		Percentage exchange			Exchange rate (ml./min.)
						Evans blue (ml.)	Fetal hemoglobin (ml.)	Plasma	Red cells	Bilirubin	
1	1,475	No	290	200	115	129	96	92	93	119	11.6
2	2,100	No	480	230	159	220	175	82	88	117	18.5
3	2,780	No	700	250	139	211	151	87	93	146	12.8
4	2,250	No	495	220	153	213	*	92	–	105	17.1
5	2,470	No	480	190	151	200	190	94	86	74	13.7
6	2,470	No	705	290	187	267	*	100	–	142	13.9
7	3,150	No	710	230	192	298	280	87	88	140	12.3
8	3,040	No	675	220	126	215	199	95	93	160	15.4
9	2,250	No	495	220	157	220	*	91	–	97	16.7
10	3,310	No	720	220	198	276	*	94	–	136	17.4
11	2,980	Yes	710	240	136	212	262	92	91	218	16.5
12	2,980	Yes	705	240	144	216	–	93	–	178	15.6
13	2,770	Yes	590	210	122	172	130	98	94	173	16.9
14	2,770	Yes	705	250	122	181	–	98	–	232	17.6
15	4,060	Yes	920	230	204	316	298	94	91	178	16.8
16	1,800	Yes	410	230	99	131	115	96	89	170	18.2
17	3,810	Yes	810	210	136	208	189	84	92	213	16.1
18	2,430	Yes	550	220	119	181	188	90	92	145	14.5
19	3,470	Yes	795	230	169	267	225	90	90	155	16.9
20	2,040	Yes	515	250	92	172	153	92	90	208	14.9

*Second exchange transfusion.

the results. In the first exchange, the fetal hemoglobin method probably gives a slightly more accurate estimate since little new fetal hemoglobin could enter the circulation in the available time.

The values obtained for blood volume as determined by the independent methods were strikingly similar (see Table II). They also agree with the figures given by Sisson[15] and Mollison[10] for normal infants. As already pointed out, the close agreement between blood volume determined by independent methods involving fetal hemoglobin and Evans blue estimation confirmed the figures presented here.

Some patients were excluded because fetal hemoglobin and Evans blue methods of determining the blood volume failed to agree. Evans blue values are taken for purposes of calculation in presenting the results in these excluded cases as shown in Table III. Results in babies with gross clotting or hemolysis of specimens are not presented. Results for those babies in the control series with inadequate exchanges are also included in Table III. None of the patients in Table III appear in the results of Table I or Fig. 1.

DISCUSSION

The results reported in this paper show that there is a striking improvement in bilirubin removal when human albumin is administered with the blood given during exchange transfusion of erythroblastotic babies.

The series of cases is still too small to evaluate the full clinical value of albumin-fortified blood transfusions, but already the results suggest that the necessity for repeated exchanges will be considerably reduced by addition of serum albumin in the early stages of exchange and maintenance of it at a high level throughout.

These effects may be explained by 1 or both of 2 mechanisms. The first possibility is that human albumin exerts an osmotic effect, expanding the plasma volume at the expense of tissue water, but in practice no elevation of venous pressure or wide variation in hematocrit value was observed. The second and more likely explanation is rapid diffusion of bilirubin into the circulation when large numbers of binding sites are made available by the addition of intravascular albumin.

The second dose of albumin given when the operation is half completed should ensure continuously favorable conditions for bilirubin diffusion throughout the whole period of the exchange. As an appreciable amount of the albumin administered must be retained in the infant's circulation, this should be of therapeutic value by providing free binding sites for unbound bilirubin entering the circulation after the period of the exchange. The use of so large a volume of albumin solution in comparison with the baby's total blood volume could be questioned on the ground that it would appreciably increase the degree of anemia. In

Table III. Exchange results for cases excluded from Tables I and II and Fig. 1

Albumin	*Plasma exchange* (%)	*Red blood cell exchange* (%)	*Bilirubin exchange* (%)	*Remarks*
No	86	81	120	Volume of exchange too small
No	92	85	88	
Yes	–	93	182	Evans blue figures not available
Yes	94	? 66	166	Fetal hemoglobin estimations not available
No	94	93	146	or unreliable because exchange was a
No	96	–	104	repeat one
No	88	–	112	
No	94	71	136	
No	93	–	144	

practice this was not a problem since the greater part is removed in the waste or diffuses into tissue fluid. A subsequent simple transfusion was needed by only 1 of the 20 babies in the series and this baby had 3 orthodox exchange transfusions.

Albumin-fortified blood transfusions should be particularly valuable in babies first seen when already deeply icteric by aiding rapid removal of the bilirubin and decreasing the need for multiple exchanges in these sick infants.

Severe anemia and cardiac failure are the only contraindications for the use of albumin. In these infants erythrocytes are the urgent need. Jaundice is not the immediate problem and the introduction of a potential volume expander in the form of concentrated human albumin may be dangerous.

There was no evidence of cardiac failure in any of the babies treated with albumin, although it is to be noted no profoundly anemic infant happened to need treatment during the time this work was proceeding.

It is noteworthy that no deaths occurred among any of the babies in either the albumin-treated or control groups although several were severely affected.

SUMMARY

1. The percentage exchange of plasma, of fetal red blood cells, and of bilirubin was determined in 20 infants with erythroblastosis fetalis.

2. In 10 of these patients salt-poor concentrated serum albumin was introduced into the exchange medium.

3. A striking improvement in extraction of bilirubin was observed in the albumin-treated group.

4. Only trivial technical difficulties were encountered.

5. No deaths occurred in either series.

6. The possible mode of action of human albumin is discussed.

7. Indications and contraindications for the use of human albumin are outlined.

We wish to acknowledge the encouragement provided by Professor S. L. Townsend and Dr. Kate Campbell. Exchange transfusions were carried out by Dr. W. I. H. Johnston and Dr. N. A. Beischer. Mrs. N. Gausis and Miss H. L. Coghlan afforded valuable technical assistance and Miss M. V. Ryan helped greatly with the manuscript. We particularly wish to acknowledge help provided by Dr. Donald B. Cheek in the planning of this investigation and by Miss B. Laby and Mr. B. L. Adkins, of the Department of Statistics, University of Melbourne, who analyzed the data.

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Diaper rash, self-inflicted excoriations, and crying in full-term newborn infants kept in the prone or supine position

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THERE is strong feeling on the part of some nursery personnel that it is important to place newly born infants in the supine position. However, there is a lack of specific information on the effect of position on neonatal morbidity. A study was initiated, therefore, to evaluate the effects of maintaining one group of newly born infants continuously during their nursery course in the prone position and another group in the supine position.

METHOD OF STUDY

Immediately on admission to the nursery newly born full-term white infants were assigned in rotation to be placed in either the prone or the supine position throughout their nursery course. The infants were kept in the same nursery and the type of diapers,† bedding, time and type of feeding, and frequency with which diapers were changed were similar in both groups of infants. Early morning feedings were at 5:30 A.M. and 9:30 A.M. Rounds were made between 8:00 and 9:15 A.M., at which time the infants were undressed and carefully examined under a bright light. Crying was noted and recorded prior to the physical examination. Erythema, macules, and papules in the diaper area were classified as diaper rash, except in patients with generalized macular-papular dermatoses extending into the diaper area.

RESULTS

The frequency of diaper rash was considerably greater in infants kept in the supine position (see Table I). The majority of the diaper dermatoses were found in the gluteal region.

The incidence of scratch marks (self-inflicted excoriations) was also considerably higher in infants kept in the supine position (see Table I). Most of the scratch marks were on the face, although a few were also noted on the trunk. Some of the excoriations were quite prominent (Fig. 1); secondary infections were not observed.

The frequency of crying was about twice

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†*Cotton diapers were used.*

Fig. 1. Full-term infant, age 2 days, with multiple self-inflicted excoriations (scratch marks).

as great in the infants kept on their backs (see Table I). When the position of the infants who were crying was reversed, over one half of the infants on their backs stopped crying when placed on their stomachs whereas only an occasional infant lying on his abdomen stopped crying when placed on his back. The relatively high incidence of crying was caused by the fact that the infants were observed shortly before feeding time.

Table I. Full-term newborn infants kept in the prone or in the supine position in the first 4 days of life: the incidence of diaper rash, of self-inflicted excoriations, and of crying

	Day of life			
	1 (%)	*2* (%)	*3* (%)	*4* (%)
Diaper rash				
140 babies on back	0	0	9.4	28.1
141 babies on stomach	0	0.8	0.8	10.3
Statistical significance of difference	–	–	1.0	0.1
Scratch marks				
140 babies on back	14.6	24.2	23.4	27.4
141 babies on stomach	9.7	10.2	19.9	19.7
Statistical significance of difference	–	1.0	–	5.0
Crying				
140 babies on back	14.6	20.5	32.0	42.2
141 babies on stomach	9.7	8.5	17.6	13.7
Statistical significance of difference	–	1.0	1.0	0.1

Table II. The incidence of diaper rash in the first 5 days of life in infants receiving 0.2 Gm. DL-methionine per day*

	Without diaper rash	*With diaper rash*	*% with diaper rash*
Control infants	47	30	64
Infants receiving 0.2 Gm. DL-methionine once a day	45	22	50†

*Diaper rash was not observed in the inguinal area or on the genitals. The diaper rash was not thought to be due to ammonia since there was no ammoniacal odor.

†The difference in incidence of diaper rash is not statistically significant.

Erythema and chafing of the skin over the knees was limited to infants in the prone position, and was considered to be clinically detrimental in 2 out of 141 infants. Erythema and chafing of the skin over the heels were limited to infants kept in the supine position and were clinically detrimental in 2 out of 140 infants. Pustules, toxic erythema, and generalized macular-papular rashes were observed in an equal number of the infants maintained in each position.

In a study still in progress it has been observed that the incidence of umbilical cord erythema is slightly higher in infants kept in the supine position, but the difference is not statistically significant.

DISCUSSION

Dermatoses, and particularly diaper rash and scratch marks, are the most frequent cause of morbidity in the newborn nursery, exceeding regurgitation in frequency. To a considerable extent these minor nuisances are preventable.

Although diaper rash can usually be prevented by frequent change of diapers, a limited nursery staff may render this unfeasible, particularly when one nurse or nurse's aide is assigned to as many as 12 to 20 babies during one or more shifts per day. Maintaining infants in the prone position reduces the incidence of diaper rash. Diaper rash is probably less frequent when infants

are in the prone position because urine and feces tend to fall away from the baby—at least feces and urine do not become compressed under the gluteal area as much. The addition of methioine to the formula did not alter the incidence of diaper rash in infants in the first 5 days of life (see Table II).

Keeping babies in the prone position reduces the number of infants with self-inflicted scratch marks. A pair of scissors should be included as one of the items to be brought to the hospital by the mother in confinement. The baby's nails should not be cut by the nursery staff, who are often overworked and who are potentially liable if they inadvertantly nick the skin, but by the mother who should learn how to cut the baby's nails.

SUMMARY

Newly born infants kept in the prone (stomach) position have less diaper rash, self-inflicted excoriations (scratch marks), and cry less than infants kept in the supine (back) position.

Otitis media in a premature infant

Otoscopic and pathologic findings

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WHILE making routine serial otoscopic examinations on premature infants with birth weights of 1,001 to 1,500 grams, we noted changes in the drum of one infant indicative of otitis media on the basis of currently accepted criteria for older infants. Because otitis media is usually not considered to occur in the very young infant, this being the first case encountered in our experience, the present report is submitted.

CLINICAL COURSE

The patient, a Negro female twin, was admitted to our hospital at 6 hours of age, weighing 1,390 grams, and in apparently fair condition.

On admission, the patient was given routine premature care.

On the eighth day, otoscopic examination revealed the following in the left ear: there were hairs in the canal and the drum showed ventral and dorsal pyrospheres,* spokelike markings,* the long process of the malleus, and pinkish-gray tensa and flaccida. There were hairs in the right ear canal and in the drum a ventral pyrosphere, spokelike markings, a dorsal gray area,* a long process of the malleus, a doubtful cone of light, a reddish-gray flaccida, and a pinkish-gray tensa. Otitis media was not suspected but, in retrospect, might have been because of the relative redness of the right flaccida.

On the ninth day six small stools with strings of red mucus were passed. The hemoglobin level at the time was 17 Gm. per cent, and a stool culture yielded no pathogens. The following day the infant became listless, refused her formula, and seemed to collect mucus in the throat. On the eleventh day the patient vomited, especially when gavaged. On physical examination she was very lethargic and did not cry. Firm loops

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"Pyrospheres"—"fireballs"—are luminous areas which vary in color from red to silver and are about the size of the short process. The one ventral to the umbo occurs more frequently than the one dorsal to it. Spokelike markings are hair-width linear markings which radiate from the umbo on the tensa ventral, and dorsal to the cone of light. The dorsal gray area occupies a portion of the drum at its crown margin dorsal to the short process (Fig. 1).

of bowel could be felt in the abdomen; these were considered to represent inspissated feces. A saline enema was given; hydration was maintained with fluids by clysis and formula by mouth.

On the twelfth day, the vomitus had a fecal odor, and for the next 4 days the patient remained inactive and listless, but had only occasional episodes of regurgitation and received most feeding by gavage. Roentgen examination of the abdomen showed gas in the bowel but no evidence of obstruction. A gastrocolic fistula was then suspected.

On the fourteenth day, pyrospheres, spokelike markings, dorsal gray areas, and long processes were not seen. Redness of the tensa and flaccida had increased more in the right drum than in the left one. A questionable cone of light was seen on the left side. The clinical impression was otitis media, more severe on the right side.

On the sixteenth day, abdominal distention was marked, although bowel sounds were heard. On the seventeenth day, both flaccidae and the right tensa were red, but the left tensa was relatively gray. No light reflexes were seen. The short process of the right drum was less well defined than the one on the left, suggesting thickening of the tympanic membrane. Therefore, on the basis of changes in appearances of the ear drums on longitudinal examinations and the contrast between right and left drums, we were convinced that our clinical impression of otitis media, more severe on the right, was justified.

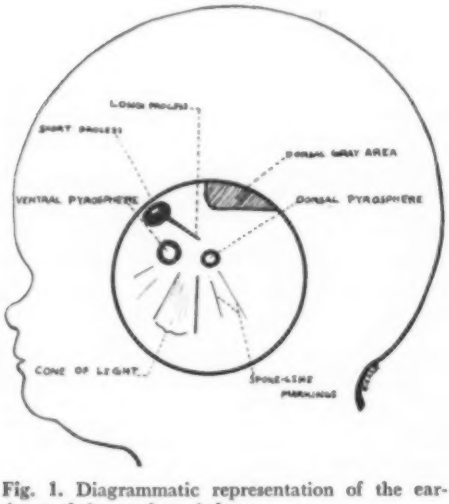

Fig. 1. Diagrammatic representation of the eardrum of the newborn infant.

Fig. 2. Photomicrograph of paraffin embedded, hematoxylin and eosin stained section demonstrating thickened tympanic membrane and purulent material in middle ear cavity. (Original magnification ×130.)

There were periods of cyanosis and the patient's condition continued to deteriorate until she died at 18 days of age. Clinical diagnoses at the time of death were: intestinal obstruction with possible gastrocolic fistula and probable purulent otitis media.

AUTOPSY FINDINGS

Gross pathology. The left middle ear cavity was opened and a light yellow sheet of castlike material was present in this space. The right middle ear was then decalcified; it contained a similar cast. Gross pathologic diagnoses were: (1) otitis media, purulent, bilateral, (2) fecal peritonitis, (3) hemorrhagic gastritis, (4) pseudomembranous

ulcerative colitis, and (5) intrapulmonary hemorrhage.

Microbiology. (Dr. G. John Buddingh.) Gram-stained sections of the decalcified right middle ear showed discrete organisms and clumps typical of *Hemophilus influenzae* on the basis of gram-negative staining, small size, scarcity in numbers, rod shapes, and pleomorphism; only this organism was seen.

Histopathologic examination. (Dr. John Dent.) Decalcified sections of the right middle ear stained with hematoxylin and eosin were studied microscopically along with similar sections from an ear of a premature infant without clinical otitis media; the tympanic membrane was thickened, and marked congestion and dilatation of blood vessels were present; a purulent exudate which filled the middle ear was composed principally of neutrophils, fibrin, and a few red blood cells; there was conspicuous desquamation of the respiratory epithelium lining the middle ear cavity, and the underlying substantia propria also showed desquamation, congestion, and edema; in several places the blood vessels of the substantia propria had ruptured; the epithelium overlying the external surface of the tympanic membrane appeared somewhat thicker than that of the other (control) ear (Fig. 2).

Histopathologic examination. (Dr. Q. R. Johnson.) Hematoxylin and eosin stained sections of the decalcified right middle ear showed a greatly thickened tympanic membrane. This was due largely to marked engorgement of the blood vessels. The stratified squamous epithelium was intact and contained the usual layers. The mucous membrane of the middle ear was not intact, there being lack of continuity, hemorrhage, and an adherent purulent exudate composed of neutrophils and monocytes. The epithelium, which varied from cuboidal to ciliated pseudostratified columnar, was not intact over the bony wall of the middle ear. Adherent purulent exudate consisted of neutrophils and monocytes. The middle ear contained much purulent exudate consisting of neutrophils, monocytes, and cellular debris. The bone, bone marrow, and external auditory canal were not remarkable. Diagnosis: acute otitis media (Fig. 2).

DISCUSSION

The otoscopic findings in the newborn healthy premature infant resemble those of the newborn term infant[1, 2] (Fig. 1). Unique signs, consisting of fireballs (pyrospheres), spokelike markings, and a dorsal gray area, are seen in both. However, the external auditory canal of the premature infant is commonly smaller. The adult landmarks, cone of light, ossicles, umbo, tensa, and flaccida, are present in the newborn infant, but have a different appearance.[1, 2] Debris is present but cerumen is lacking and the middle ear landmarks of the incus, stapes, and round window are not characteristically seen by otoscopy; physical signs of disease, to our knowledge, have not been carefully described.

The otitis media was not treated with antibiotics; DeToni,[3] after several years' experience in the treatment of otoantritis in premature infants, finally decided that antibiotic therapy was ineffectual.

Although bacterial cultures were not available, bacteria were found in the gram-stained sections of middle ear pus as objective evidence of infectious otitis media.

SUMMARY AND CONCLUSION

Bilateral purulent otitis media in a small premature infant has been observed. Diagnosis was made otoscopically during life, and confirmed later by gross and microscopic pathologic observations. Insufficient knowledge of the normal appearance of the ear of the premature infant is a diagnostic handicap. A study correlating otoscopic, microbiologic, and pathologic observations in a large series of premature infants is planned.

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Intrauterine constriction band

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A CONSTRICTION groove on the peripheral part of a limb due to an abnormality of the amnion is a rare congenital anomaly. The following outlines such a case.

CASE DESCRIPTION

The infant was a white male delivered at 41 weeks' gestation following a normal pregnancy. Presentation was a vertex and delivery was effected by low forceps. The mother was a gravida v, para iv. Her other children had no evident congenital abnormalities. The birth weight was 9 pounds, 13 ounces, and the Apgar rating was 9 at 1 minute, 10 at 5 minutes. At delivery it was noted that the baby had a tight constriction ring completely encircling the right calf about 4 cm. above the ankle joint (Fig. 1). The furrow was of equal depth and width throughout, being about 2 mm. deep and 1.5 mm. wide; the overlying skin was paler, smoother, and shinier than the skin above and below it. The skin over the rest of the body showed slight desquamation and dryness. There was considerable edema and blueness of the leg and foot below the constriction. Sensation to pain and touch distal to the constriction appeared to be normal. There were no trophic changes of the leg and foot. The blood supply to the tissues below the constricted area appeared to be unimpaired as the color improved spontaneously shortly after delivery. Lymphatic drainage, however, was thought to be impaired because the edema of the foot persisted for 6 weeks. When the edema subsided, the dorsalis pedis and posterior tibial arteries were palpable.

Examination of the placenta showed, on the fetal surface, a small sac just large enough to contain the foot and lower leg up to the level of the constriction. The sac had a semicircular, double band of amniotic membrane at its free edge (Fig. 2). The free edge was smooth and shiny, and resembled the rest of the normal-appearing amniotic membrane. It would appear that, during intrauterine existence, the foot had been enclosed in the sac and that the free edge of amniotic membrane had caused the constriction ring. The infant was discharged on the eighth day when the leg and foot appeared normal except for the constriction already described.

The band was operated on when the infant was 9 months of age. The appearance and size of the affected limb were normal except for the band and did not differ from those of the other side. The amniotic band was removed in stages by a multiple x-plasty procedure. The band was attached to the deep fascia and it was felt that circumferential removal in toto might jeopardize the circulation distal to the constriction.

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Fig. 1. Right leg showing constriction groove.

Fig. 2. Tip of scissors entering mouth of collapsed sac.

Section showed skin with fibrosis in the lower corium. The epidermis showed some irregularity in epidermal thickness, with slight papillomatosis and hyperkeratosis. The appearance was that of a fibrous cutaneous band.

DISCUSSION

A case resembling the one described above was reported by Barenberg and Greenberg[1] in 1942. In their case, there were sensory disturbances distal to the groove with ulcerations and delayed healing following the slightest trauma. There is no satisfactory explanation for the occurrence of constriction grooves associated with amniotic bands. According to Streeter[2] no definite evidence has been presented to show that the amnion itself or the amniotic fluid is involved. Streeter concluded, after an exhaustive study, that intrauterine constriction bands are due to a primary constitutional defect of the germ plasm which resulted in defective growth of the area of tissue affected. The annular zones are usually not sufficiently deep to interfere significantly with the circulation.

In this case the amniotic sac displaced a volume of fluid equal to that displaced by the leg and foot distal to the groove; this, together with the fact that the neck of the sac exactly fitted the groove in the leg, would suggest that the constricting effect of the amniotic sac prevented the normal development of the ectoderm and, possibly, the mesoderm in the area occupied by the furrow. The circulation, the sensory and motor nerves, and the underlying bone were not affected. It is concluded that the groove developed as a result of pressure by the neck of the amniotic sac at a time when the development of the arteries, nerves, and bone was already completed.

SUMMARY

A case of intrauterine constriction band in which the annular groove on the lower leg was associated with a close-fitting amniotic sac is described.

The author wishes to thank Dr. W. D. Frew of the Department of Obstetrics and Dr. W. C. Taylor of the Department of Paediatrics for permission to publish this case, Dr. J. D. M. Alton, of the Department of Surgery, for the operation report, and Dr. J. W. McGregor, of the Department of Pathology, for the histology report.

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Incomplete differentiation of the aortic valve (myxomatosis)

A cause of myocardial infarction in the neonate

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CRAIG,[1] in an excellent review, reported the findings in 37 cases of congenital heart disease with thickening of the ventricular mural endocardium. In the majority of these cases, there was an associated thick malformation of the valves. An additional 6 cases were presented with similar defects in the valves but without mural endocardial involvement. In the great majority of the latter cases the site was the pulmonary valves, next most frequently the tricuspid valve, and in only a single instance the aortic valve. In Manion's[4] experience, however, all valves or any valve may be involved without the endocardial wall. In cases with associated mural endocardial thickening the lesion was fibroelastosis. The valvular component was that usually designated as "fetal endocarditis."[2] Gross[3] and Craig[1] point out that this term is unsatisfactory, and they offer arguments against the concept of infection as the etiological factor. As suggested by Manion,[4] the term "incomplete differentiation of the valve (myxomatosis)" is preferable in that this connotes the basic lesion of the valvular defect. It is the purpose of the following report to illustrate the association of isolated incomplete aortic valvular differentiation with cardiac hypertrophy and myocardial infarction in the neonate. Little mention is made in the literature of such an association, and in some reviews of myocardial infarction or of cardiac hypertrophy in the neonate no statement is made concerning this abnormality.[5]

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REPORT OF CASES

Case 1

Clinical history. This infant was born Oct. 30, 1958. During the 9 months of gestation, the mother was well. A 10-hour labor was terminated by vaginal delivery of an 8 pound, 12½ ounce normal-appearing Caucasian male. Respiration was spontaneous. In the nursery, a Grade II/VI harsh systolic murmur was heard over the precordium loudest at the base. The murmur was trans-

Fig. 1. Case 1. Thickening and stenosis of aortic valve with marked left ventricular hypertrophy.

mitted to the neck vessels. Clinically, no cardiac enlargement was discernible. The remainder of the physical examination was normal. Feedings were instituted without incident, and there was no cyanosis or respiratory distress. After discharge, the infant progressed satisfactorily. All feedings were taken eagerly. The infant was very active, and the parents noted no respiratory distress or cyanosis. At 6 weeks of age, he was seen in the clinic for a routine examination.

Physical examination at 6 weeks of age. His weight was 11 pounds, 3 ounces; his height, 23 inches. The infant was well nourished and active. No cyanosis was present. Motor development was normal. There was a Grade III harsh systolic murmur, again heard loudest at the base of the heart, transmitted to the neck vessels. No thrills were palpable. The aortic second sound was present. No cardiac enlargement was noted. The lungs were clear to auscultation. The liver and spleen were not enlarged.

Laboratory findings. An electrocardiogram disclosed an axis of 90 degrees and a sinus tachycardia of 180. There was no electrocardiographic evidence of infarction or left ventricular hypertrophy. An x-ray of the chest was normal.

Course. The infant continued to do well until 2½ months of age when he suddenly developed a vesicular eruption of the left flank and abdomen. Because of the rash he was brought to the clinic. Examination disclosed small vesicles closely spaced, confined to the abdomen and left flank. The murmur was again noted and considered to be unchanged from the examination at 6 weeks of age. Since the infant was active and in no distress he was sent home with a diagnosis of "contact dermatitis." No medication other than a drying skin lotion was given. The following morning the infant refused his early feeding and appeared very lethargic. On the way to the hospital he died.

Necropsy findings of the heart. The weight was 77 grams (normal 23 grams). The pericardial surface had numerous petechiae, most prominent about the sulci. A probepatent ductus arteriosus was present which measured 1 cm. in length and approximately 0.2 cm. in greatest diameter. The foramen ovale was anatomically closed. No interventricular septal defects were present. The tricuspid valve, the pulmonary valve, and the mitral valve had the normal number of cusps, all of which were soft and velamentous. The aortic valve was moderately thickened, and there were small verrucoid glistening gray-white elevations. Upon examination of the valve from the ventricular surface there appeared to be only 2 cusps, each of

Fig. 2. Case 1. Abundant myxomatous tissue constitutes the aortic valve. (Hematoxylin and eosin. Original magnification ×332.)

Fig. 3. Case 1. Necrosis of left ventricular papillary muscle. Focal calcification is evident. (Hematoxylin and eosin. Original magnification ×332.)

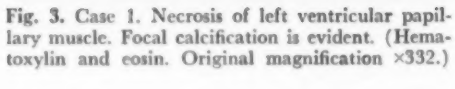

Fig. 4. Case 2. Thickening and stenosis of the aortic valve.

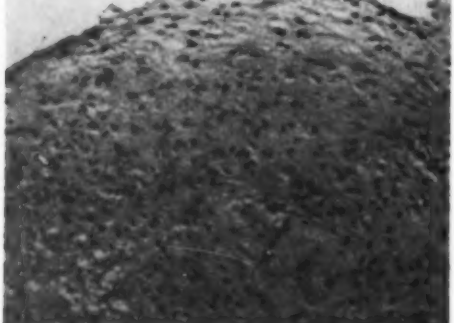

Fig. 5. Case 2. Embryonic myxomatous tissue constitutes the aortic valve. (Hematoxylin and eosin. Original magnification ×1,064.)

which measured approximately 1 cm. in greatest diameter. However, on examination from the aortic surface there appeared to be 2 raphes. These separated 3 cusps, 2 of which measured approximately 0.5 times 0.5 cm., while the noncoronary cusp measured approximately 1 cm. in greatest diameter. The coronary arteries appeared to have a normal origin. In addition to small verrucoid elevations along the free margin, over-all thickening and stenosis were present (Fig. 1). The left ventricular myocardium measured 0.8 cm., and the right ventricular myocardium measured up to 0.2 cm. in greatest thickness. When the interventricular septum and other portions of the left ventricular myocardium were sectioned, slight focal softening together with light brown discoloration was evident.

Microscopic sections through the aortic valve revealed the presence of abundant fibrillary embryonic-appearing tissue (Fig. 2). The nuclei frequently were spindly or stellate. In general, the staining was basophilic. In only a few areas could definite collagen production be identified. Elastic tissue was not present. Sections taken through the left ventricular myocardium showed no subendocardial fibroelastosis. Pronounced myocardial ischemic changes involving the papillary muscles and subendocardial tissue were present, with large areas presenting pronounced vacuolation and loss of striation. In some fields, there were wide areas of eosinophilic necrosis. Focal calcification was conspicuous (Fig. 3). In a few areas, aggregates of mononuclear inflammatory cells were observed.

Case 2

Clinical History. This infant was born Oct. 7, 1959. The 9 months' gestation of the 22-year-old gravid i, para 0, mother was complicated by an episode of hyperemesis during the sixth week. Four days prior to the estimated date of confinement, an 18-hour labor was terminated by vaginal delivery of a 7 pound, 13 ounce Caucasian female. Respirations were established quickly, and the immediate neonatal course was uneventful. In the nursery, the infant took all feedings

well, and no respiratory distress or cyanosis was noted. The examining physician noted a Grade III to IV harsh systolic murmur, loudest at the base of the heart. Blood pressure in the right arm was 88 systolic and in the right leg 94 systolic. The remainder of the examination was within normal limits. An electrocardiogram and chest x-ray obtained at age 24 hours were considered normal. The infant was discharged at 4 days of age and was seen again when she was 2 weeks old. The mother reported no feeding difficulties, cyanosis, respiratory distress, or excessive crying.

Physical examination at 2 weeks of age. Her weight was 8 pounds, 5 ounces, her height, 22 inches. The infant was active and had good color. The harsh Grade III systolic murmur was again noted. The murmur was loudest at the aortic valve area, transmitted well to the neck vessels and to both shoulders. It was not audible over the back. No thrills were palpable. No cardiac enlargement was discernible. The blood pressure in the right arm and right leg was approximately the same as noted in the nursery. The femoral arteries were palpable. There was no enlargement of the liver or spleen. The lungs were clear to auscultation. The remainder of the examination was normal.

Laboratory data. An electrocardiogram obtained at the age of 2 weeks disclosed an axis deviation of plus 110 degrees and a rate of 180. There was no evidence of left ventricular hypertrophy or myocardial ischemia. An x-ray disclosed no evidence of cardiomegaly.

Course. The infant continued to do well until the age of 1 month. At that time, she developed rhinorrhea and anorexia. After several days, she suddenly became lethargic and refused all feedings. Grunting respirations were noted, and she was brought to the clinic approximately 10 hours after onset of the lethargy. The examining physician noted marked cyanosis and limpness. The infant died 22 minutes after arrival at the hospital.

Necropsy findings of the heart. The heart weight was 65 grams (normal 20 grams). Numerous pericardial petechiae were present and were most prominent posteriorly about the sulci. The ductus arteriosus was patent and measured 0.5 cm. in length. The foramen ovale was anatomically closed. No interventricular septal defects were present. The tricuspid valve, pulmonary valve, and the mitral valve all had the normal number of cusps and were soft and velamentous. The mitral valve measured 2.5 cm. in circumference, the pulmonary valve 2.5 cm., and the tricuspid valve 4.0 cm. The aortic valve consisted of 2 cusps, with both cusps being of approximately the same size. The entire valve measured 1.7 cm. in circumference. It was moderately thickened, with small verrucoid elevations along the free margin. The verrucoid nodularities were glistening and gray-white and had a soft consistency (Fig. 4). The anterior cusp was somewhat triangular in shape. Both coronary artery orifices were related to the anterior cusp. There was normal distribution of the coronary arteries. The left ventricular myocardium measured approximately 0.8 cm., and the right ventricular myocardium measured 0.3 cm. in greatest thickness. The entire left ventricular myocardium, including the interventricular septum, was soft and flabby and, upon sectioning, had a distinct gray overcast with red speckling throughout. This change was most pronounced at the apex, although it could be identified throughout the left ventricular myocardium.

Microscopic study of the heart revealed within the left ventricular myocardium a predominant subendocardial localization of ischemic myocardial changes in the form of conspicuous small vacuolations of muscle fibers. Some areas of eosinophilic homogenous staining due to loss of nuclei and striations were seen. Also noted, in a few areas, was moderately dense collagen, representing foci of scarring. Hyperemia was conspicuous throughout. In one papillary muscle, a small focus of calcification could be identified. In portions of the heart, where the myocardium was intact, the muscle nuclei were hypertrophied and hyperchromatic. In only a few areas could mononuclear cellular infiltrates be identified. Subendocardial fibroelastotic

thickening was not evident. Sections taken through the aortic valve revealed throughout, with the exception of the valve base, the presence of an embryonic type of connective tissue with a basophilic fibrillary stroma which had spindly nuclei, sometimes stellate in shape (Fig. 5). In only a few areas could collagen bundles be identified. Elastic tissue was absent.

DISCUSSION

The clinical pictures of these two cases of isolated incomplete differentiation of the aortic valve were similar. In each, the harsh murmur which seemed to arise from the aortic valve area was noted from birth. An electrocardiogram and chest x-ray at the age of 6 weeks in Case 1 and at the age of 2 weeks in Case 2 were normal. No cyanosis, respiratory distress, feeding difficulties, or episodes suggestive of chest pain were reported by the parents. Each infant had a short period of illness characterized by lethargy and refusal to feed for approximately 10 hours before death. The aortic valves were bicuspid, warty, and stenotic. Microscopic study revealed the valvular defect to be in both instances due to the presence of abundant myxomatous tissue. Extensive old and recent infarction of the myocardium was evident. In neither case could microscopic evidence of infection within the heart or in other tissues be identified.

The anlage of the cardiac valves consists of embryonic connective tissue. Overproduction of this tissue arising from the endocardial layer may account for the abundant myxomatous tissue throughout the aortic valves noted at autopsy. Another explanation is failure of gradual transformation of the bulk of this embryonic tissue into the denser connective and elastic tissue of the normal infant aortic valve. The myocardial degenerative changes are interpreted as ischemic in origin. Craig[1] believed that the aortic valvular stenosis per se would give rise to a reduction in the volume of coronary blood flow. Manion[4] feels that the reduction in volume of coronary flow with consequent myocardial ischemia is caused by poor functioning of the valve.

SUMMARY

Two instances of moycardial infarction in the neonate with associated incomplete differentiation of the aortic valve are described. Consequent to persistence of aortic valvular embryonic tissue with poor functioning of the valve, coronary arterial inflow was jeopardized with resultant myocardial ischemia.

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Congenital Letterer-Siwe disease (reticuloendotheliosis) in a term stillborn infant

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ACUTE and chronic disturbances involving the reticuloendothelial system are of particular interest because of their obscure etiology, multifaceted clinical patterns, and similarities in pathologic changes. Most of these diseases defy clear classification. They are variously considered to be metabolic, infectious, or neoplastic in origin.

Of special interest to physicians who care for infants and children are three disturbances involving the reticuloendothelial system: eosinophilic granuloma, Hand-Schüller-Christian disease, and, most particularly, Letterer-Siwe disease because of its rapid and usually fatal course. These three have been regarded by most observers as variations of the same fundamental disease process, having possibly the same etiology and a basically similar pathogenesis, the primary disorder consisting of a proliferative response of reticulum cells to an unknown stimulating agent.

The particular situation to be described is unique and so far as can be ascertained has not been reported heretofore in a term stillborn infant.

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CASE REPORT

Mrs. G. S. (No. 58-39010), aged 25 years, presented herself to colleagues* in another community on July 12, 1957, for prenatal care in her first pregnancy. The family history disclosed malignant disease in a paternal grandmother and in one maternal and one paternal great-aunt. The patient's mother had 3 pregnancies, with no fetal abnormalities. The medical history did not reveal any childhood diseases except pyelitis at 5 years of age and no serious illnesses since she was grown. The menses were normal, the last menstrual period on April 26, 1957. The family and medical histories of the husband (aged 40) were negative.

Physical examination revealed a young, normally developed woman in good health. Her weight was 137 pounds, and the blood pressure was 120/70. Pelvic examination confirmed the presence of an intrauterine pregnancy of 8 weeks' duration. The red blood cell count was 5.9 million; the hemoglobin was 14 Gm. (86 per cent); and the white blood cell and differential counts were within normal limits. The basal metabolic rate on Sept. 17, 1958, was minus 6. The Wassermann reaction was negative; her blood group was O and she was Rh positive; urinal-

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Figs. 1 and 2. Note the widely distributed hemorrhagic, crusted, or scaling nodules. The slipping of the skin is a postmortem change.

ysis was normal. In the third month of pregnancy she was given an injection of poliomyelitis vaccine, followed by a second one a month later; in the sixth month she received 200 units of "Asiatic flu" vaccine. The patient then moved to Seattle and came under the observation of the senior author on Nov. 27, 1957. She continued to pursue a normal course and entered Swedish Hospital on Jan. 28, 1958, in early labor, the membranes having ruptured shortly before admission. No fetal heart tones could be heard, and no fetal activity was observed. She commented that life had not been felt for about a day. Upon vaginal examination, palpation of the fetal scalp revealed a number of small, firm, cutaneous nodules, the significance of which was not understood at the time. Pelvic x-rays had been secured earlier in labor; the bones of the fetal skull appeared less thick than was expected. After approximately 22 hours of labor, delivery was accomplished. The infant was a stillborn male, estimated to weigh 8 pounds. A striking feature was the presence of innumerable, widely scattered circumscribed skin lesions, consisting of intracutaneous and subcutaneous bluish-red hemorrhagic nodules varying in size from 0.25 to 1.5 cm. in diameter and a macular, purpuric type of rash in focal areas. The liver was enlarged. There was no adenopathy. The placenta appeared normal.

Anatomic findings. The body was well developed and nourished, weighing 3,310 grams and measuring 43 cm. in length. There was slipping of the epidermis and overriding of the flat bones of the skull. On the skin there were numerous widely distributed, firm, hemorrhagic nodules elevated 0.5 to 1.2 cm. without characteristic grouping. Some of these were superficially ulcerated; a few were covered by macerated white scales (Figs. 1 and 2). The oral mucosa appeared normal. There was an estimated 2 c.c. of thick sanguineous fluid in the peritoneal cavity and approximately 10 c.c. of

similar fluid in each pleural cavity. The heart weighed 22 grams and was grossly normal for a newborn infant. The right lung weighed 50 grams and the left lung 38 grams. Each was firm and rubbery. There were firm, nonencapsulated, moderately well-circumscribed nodules measuring up to 0.4 cm. in diameter scattered through the parenchyma; they were common in subpleural locations. When cut across they had a granular whitish appearance and bulged above the adjacent parenchyma. The bronchi were frequently obliterated or narrowed by these lesions. The spleen weighed 21 grams. The capsule was purple, slightly wrinkled, and the pulp was soft, red, and without markings. The stomach, esophagus, small and large bowel were grossly normal. The pancreas was soft, pink, and lobulated. The liver weighed 175 grams; the smooth, glistening, dark-red surface contained several firm, circumscribed nodules measuring up to 0.3 cm. in diameter. The cut surface was dark red and without markings. The gall bladder and ducts appeared to be normal. The adrenal glands were soft but otherwise unremarkable. The right and left kidneys weighed 20 and 24 grams, respectively; they were lobulated and grossly normal. There were prominent soft pink lymph nodes throughout the thorax and abdomen. These measured up to 0.4 cm. in diameter. The examination of the brain was unsatisfactory because of postmortem changes in the cerebral tissues. The placenta weighed 520 grams; there were no remarkable features.

Histologic descriptions. Lesions were observed in the skin, lungs, liver, spleen, lymph nodes, thymus, and bone. Postmortem changes were advanced in some organs but in the adventitial structures, such as lungs and skin, the tissues appeared surprisingly intact. The basic lesions were similar wherever observed and consisted of a proliferation of reticuloendothelial cells varying markedly in appearance and size (Figs. 3 and 4). The smaller forms had a diameter of 15 to 25 μ while some of the larger multinucleate giant cells exceeded 60 μ in diameter. The smaller cells were usually rounded with only a moderate amount of pink-stained cytoplasm and a round, hyperchromatic nucleus which usually contained a distinct nucleolus. Some nuclei were irregular in out-

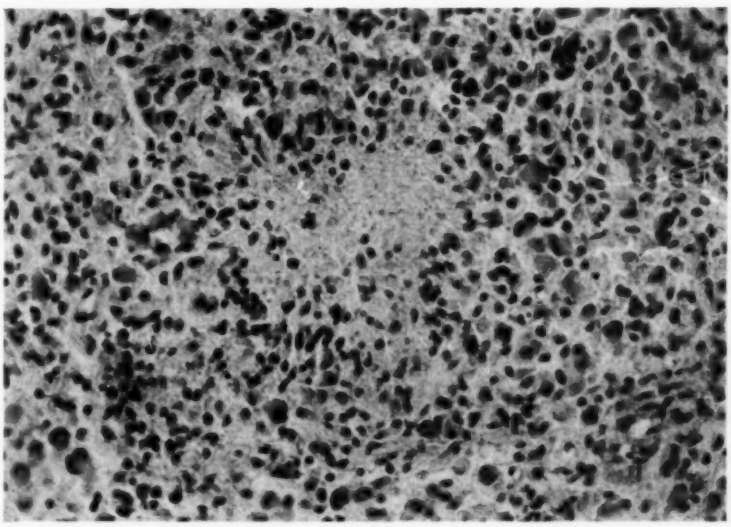

Fig. 3. Lung. The proliferating reticuloendothelial cells are arranged about a central necrotic zone. (×250; reduced ⅓.)

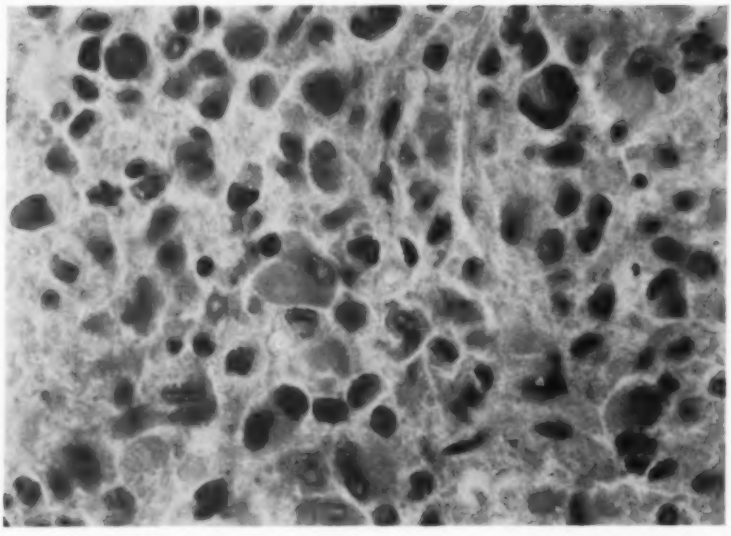

Fig. 4. Oil immersion field from lesion depicted in Fig. 3. The marked pleomorphism of the reticuloendothelial cells is apparent. (×1,200; reduced ⅓.)

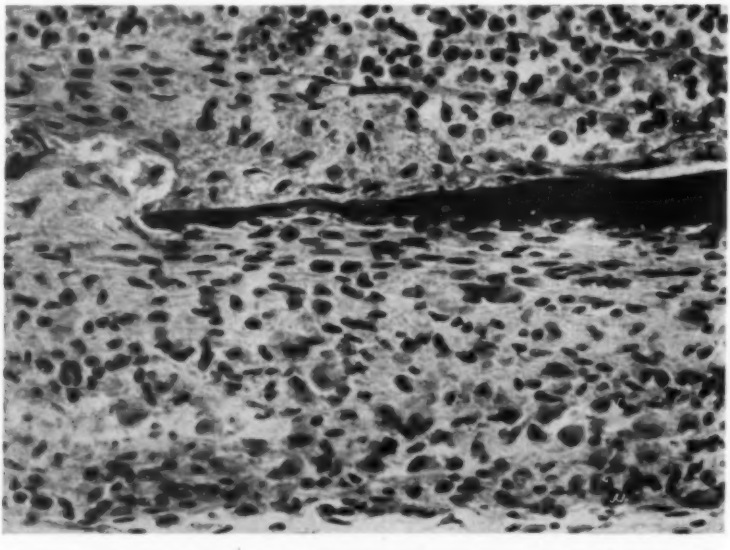

Fig. 5. Bone. In the lower half of the illustration there are subperiosteal collections of reticuloendothelial cells with erosion of the adjacent cortical bone. The marrow above and to the right consists of normal hematopoietic elements. (×300; reduced ⅓.)

line or elongate. The larger cells had abundant cytoplasm usually with vesicular nuclei that varied in contour from oval to round, indented or lobulated. In these cells nucleoli were prominent. Occasionally, giant cells were seen with a few to as many as 40 nuclei. Evidence of phagocytic activity was noted in some cells in the form of intracyto-

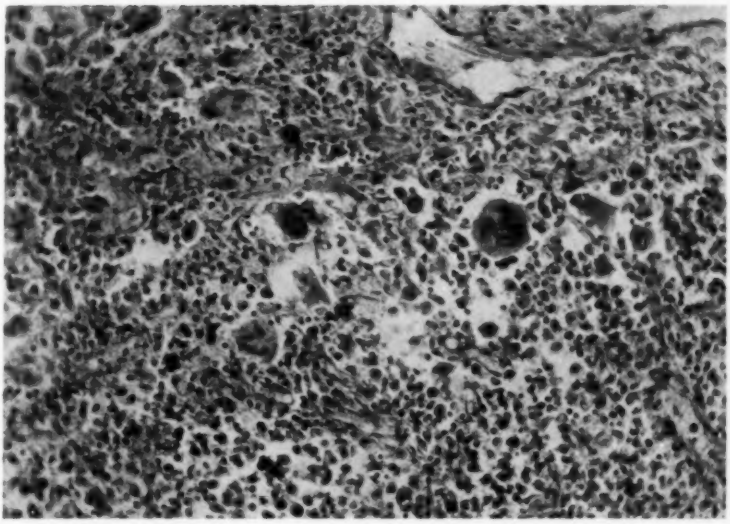

Fig. 6. Thymus. Note the multinucleate giant cells. (×200; reduced ⅕.)

plasmic red blood cells or granular debris. Cells in general lay in compact masses, but loosely knit infiltrations were noted. Necrosis was prominent. Evidence of hemorrhage, old and recent, was apparent in scattered areas. A few lymphocytes, eosinophils and neutrophilic leukocytes were observed in some of the lesions.

In the skin, the process involved the corium from the epidermis to the superficial subcutaneous fat. The overlying epidermis, though generally represented by only its deeper layers, was hyperkeratotic in a few instances. Other lesions were ulcerated. In the lungs, the process replaced large portions of a given lobe. Some bronchi were obliterated or markedly narrowed as a result of extensive mucosal involvement. The spleen was extensively autolyzed but contained prominent reticulum cells scattered throughout. Postmortem changes were advanced in the liver but islands of hematopoiesis could be identified. The striking change in the bone was an extensive subperiosteal involvement (Fig. 5). Cortical bone beneath these lesions was thin and irregularly eroded. The marrow was poorly preserved. Chondral bone formation appeared to be normal. Large multinucleate giant cells marked the process in the thymus (Fig. 6). Varying degrees of autolysis had taken place in the heart, gastrointestinal tract, pancreas, kidneys, bladder, and brain. No pathologic changes were seen in these structures. The placenta was well preserved and showed no significant change.

REVIEW OF THE LITERATURE

It does not fall within the scope of this paper to delve into any extensive discussion of the historical and clinical aspects of the reticuloendothelial diseases, but brief reference should be made to three pertinent original papers relevant to Letterer-Siwe disease. In 1924 Letterer[1] reported an acute and fatal illness in a 6-month-old infant characterized by splenomegaly, hepatomegaly, lymphadenopathy, and fever, in which there was a generalized proliferation of the reticuloendothelial tissues. In 1933 Siwe[2] reported a case and reviewed the only 4 cases reported to that time. He grouped them into an entity or syndrome characterized by hepatosplenomegaly; adenopathy, seemingly

noninfectious in origin; hemorrhagic diathesis, manifested chiefly by petechiae, exanthema, purpura, and anemia; and diffuse nonlipid reticuloendothelial cell proliferations, which focally assumed tumorlike masses in the spleen, liver, lung, lymph nodes, thymus, skin, and bone marrow. In some instances there were localized skeletal tumor formations. Biopsies of the dermal lesions, of the lymph nodes, or of the bone tumors revealed changes characteristic of reticuloendotheliosis. Siwe also pointed out that the etiology was unknown, that the disease was neither hereditary nor familial in character, and that it pursued an acute and moderately febrile course in infants and young children and terminated fatally. In 1936 Abt and Dennenholz[3] reported comparable cases and applied the term "Letterer-Siwe Disease." Numerous other papers[4-19] point up some of the confusing clinical characteristics and varying interpretations which have been placed upon the pathologic changes observed in reticuloendotheliosis occurring in different age groups.

To date approximately 100 cases of Letterer-Siwe disease have been reported, most of them during the last decade. It is pertinent to cite briefly those in which evidence of the disease has been seen in newborn or very young infants.

In 1949 Schafer[20] reported 3 cases. In one of these a cutaneous eruption was noted at birth; the infant became acutely ill at 2½ months of age and died 2 months later. Autopsy findings confirmed the clinical diagnosis. In a second case diffuse petechiae were noted at birth which disappeared following administration of vitamin K. Acute symptoms, including recurrence of petechiae and dermal lesions developed at 6 months, and death occurred at 8 months of age. The diagnosis of Letterer-Siwe disease was confirmed at autopsy. The third case was a term infant who at birth had generalized cutaneous eruptions which cleared almost completely during the first week of life; acute symptoms developed and death occurred at 6 weeks of age. Autopsy confirmed the diagnosis of reticuloendotheliosis, which was probably Letterer-Siwe disease.

In 1953 Bass,[21] reporting on the use of cortisone in the treatment of reticuloendotheliosis in children, stated that he had observed a family in which 3 children born succcessively to the same parents died in early infancy with typical symptoms and pathologic changes of Letterer-Siwe disease, but details were not given

More recently, in 1955, Batson, Shapiro, and Christie[22] described 15 additional cases of acute nonlipid disseminated reticuloendotheliosis (41 having been reported up to that time); one of their patients was a 5-month-old infant who was noted at birth to have generalized skin lesions which disappeared after a week. The infant subsequently developed typical symptoms of Letterer-Siwe disease and died at 7 months. Another case was that of a 4-week-old infant who had abdominal enlargement for one week and died at 6 weeks; the diagnosis of acute disseminated reticuloendotheliosis was confirmed at autopsy. A third case was that of a baby who was noted to have a rash on her arms the first day of life, and at 5 months had symptoms of Letterer-Siwe disease. Biopsies of skin and lymph nodes showed lesions typical of acute disseminated reticuloendotheliosis. She was treated with antibiotics and was doing well at 17 months of age.

In 1956 Hamil[23] reported 18 cases of reticuloendotheliosis including 4 diagnosed as Letterer-Siwe disease. The youngest of these patients was a 16-month-old child with a history of a skin rash developing at 3 months of age with subsequent signs and symptoms of Letterer-Siwe disease, which was confirmed by biopsies of skin and lymph nodes and by bone marrow studies. Treatment consisted of radiation therapy for the osseous lesions, antibiotics, cortisone, and ACTH. The child was doing reasonably well at 2½ years of age.

In 1957 Blum and Wohl[24] reported a case of Letterer-Siwe disease in a 20-month-old infant, in whom the course was rapidly fatal. Skin and lymph node biopsies were obtained,

but there was no postmortem examination. They suggest that this disease is neoplastic in origin.

In 1956 Avery, McAfee, and Guild[25] reported upon 40 patients with reticuloendotheliosis, 2 of whom were infants with Letterer-Siwe disease. The disease was fatal in each case; in one the onset was at 5 weeks of age with a papular rash; death occurred at 8 months.

In 1957 Frommer[26] reported Letterer-Siwe disease in a 7-week-old infant in whom a skin rash had developed at 3 weeks of age. There was some apparent early success with treatment with prednisone, but death occurred at the age of 1 year.

SUMMARY AND COMMENT

An instance of reticuloendotheliosis, confirmed at autopsy by gross and microscopic evidence of an advanced stage of the disease, is described in a term infant who died shortly before the onset of labor. The pathologic changes were no different from those observed in liveborn infants who had suffered the characteristic clinical course of the disease. Had this infant been born alive, there is little doubt that a diagnosis of congenitally acquired Letterer-Siwe disease would have been made. The parents had been healthy and the pregnancy followed a normal pattern with no evidence of maternal infection, metabolic disorder, neoplastic disease, toxemia, or other obstetric complication. Since no other reason for intrauterine death was discernible it seems reasonable to conclude that the disease resulted in the death of the fetus.

Whatever etiological factors are involved in the development of this disease, this case clearly demonstrates that these may be active in utero. Infection, either maternal or fetal, does not seem to have played a role, although this possibility cannot be entirely eliminated since numerous instances of occult infection in utero have been recognized. A deleterious influence on the fetus from the poliomyelitis and Asiatic influenza vaccines administered to the mother may be considered, but it seems most unlikely.

Case histories of babies who died in early infancy from Letterer-Siwe disease have been briefly reviewed. Some of these infants had only mild skin rashes at birth which in some instances cleared and in others remained or recurred as part of the eventual development of the complete clinical pattern of the disease. No report could be found of well-established pathologic changes characteristic of this disease in a stillborn infant. On the basis of time of onset, this case appears to complete a spectrum which includes: (1) the usual instances of this disease in which the babies appear normal at birth, (2) babies who at birth show some evidence of the disease, such as a characteristic rash, and (3) this example, possibly the first to be reported, of congenital Letterer-Siwe disease which completed its entire course in utero.

Since this report has been compiled, the mother of the stillborn infant has had two subsequent pregnancies with delivery of a normal male baby on March 31, 1959, and a normal female baby on June 3, 1960.

We wish to thank Mr. Bernard Y. Flageolle for the preparation of photographs and photomicrographic material.

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MEDICAL PROGRESS

Idiopathic respiratory distress syndrome of the newborn

An international exploration

Arnold J. Rudolph, M.D.,* and Clement A. Smith, M.D., Editors**

BOSTON, MASS.

AN INFORMAL discussion of hyaline membrane disease or the respiratory distress syndrome was held on July 21, 1959, at the IX International Congress of Pediatrics in Montreal.

The following were the participants:

Dr. E. K. Ahvenainen, Jyvaskyla, Finland
Dr. Virginia Apgar, New York
Dr. Peter Auld, Boston and Montreal
Dr. Mary Ellen Avery, Baltimore
Dr. Heinrich Baar, Pownal, Maine
Dr. Kurt Benirschke, Boston
Dr. Eric Burnard, New York
Dr. Albert Claireaux, London
Dr. Stewart Clifford, Boston
Dr. Myron Cohen, Baltimore
Dr. Charles Cook, Boston
Dr. Beryl Corner, Bristol
Dr. John Craig, Pittsburgh
Dr. V. Mary Crosse, Birmingham
Dr. Murdina Desmond, Houston
Dr. Shirley Driscoll, Boston
Dr. James Drorbaugh, Boston
Dr. Douglas Gairdner, Cambridge
Dr. Peter Gruenwald, Baltimore
Dr. John Hubbell, Boston
Dr. L. Stanley James, New York
Dr. Petter Karlberg, Stockholm
Dr. Jacob Kay, Houston
Dr. R. James McKay, Burlington
Dr. Herbert Miller, Kansas City
Dr. Alexandre Minkowski, Paris
Dr. Gerald Neligan, Newcastle-upon-Tyne
Dr. Helen Reardon, Philadelphia
Dr. Arnold Rudolph, Boston and Johannesburg
Dr. Sydney Segal, Vancouver
Dr. Clement Smith, Boston
Dr. Peter Tizard, London
Dr. Robert Usher, Montreal
Dr. David Weintraub, Buffalo

DR. RUDOLPH. Several of us have been disturbed by the lack of agreement as to exactly what different clinics mean by hya-

**Dr. Arnold J. Rudolph, the prime mover in this session, edited the tape-recorded typescript so as to preserve the informal spirit of the evening. Address, Box 7242, Johannesburg, South Africa.*

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line membrane disease, respiratory distress, pulmonary syndrome, and other terms. In this international group, we might not only get some sort of definition, but also make some clinical assessment of severity so that workers from various places could more accurately compare their data, especially as to treatment. Even if we cannot agree on these subjects, it should be worth while to hear everyone's views. I have prevailed on Dr. Smith to take the chair.

DR. SMITH. Thank you, Dr. Rudolph. To get us started, I am going to ask Dr. Miller, Dr. Crosse, and Dr. Benirschke each to speak for about 10 minutes. I hope each of them will give his or her concept of three questions:

1. Can a *clinical* diagnosis of the hyaline membrane syndrome or hyaline membrane disease be arrived at?

2. Can we agree on a classification of degree of severity so that workers can better compare the results of their attempted therapy, and

3. For evaluation of therapy, can we agree on principles of prognosis, especially as to which cases will usually be followed by recovery and which will never be?

DR. MILLER. It is important that somebody try to define hyaline membrane disease clinically, but I do not believe I can do it. I hope somebody here can, or will. We must distinguish between hyaline membranes as one large component of the respiratory distress syndrome on the one hand and the over-all picture of respiratory distress on the other. The two are not synonymous. Pulmonary hyaline membranes are a part of the respiratory distress syndrome. I hope each speaker tonight will clearly tell us which one he is talking about. We have tried for about five years to distinguish between babies with respiratory distress and those who are normal. We do not have a complete answer but we have made some progress. The respiratory rate is a very considerable help but cannot be used alone in all instances to diagnose respiratory distress. I think the baby who is free of cyanosis a few minutes after birth and continues to have a respiratory rate around 35 to 45 per minute will not die during the first week after birth regardless of birth weight.

There are one or two important matters that I should like to call attention to. It seems to me that we should all be using a uniform period as the time during which perinatal factors are operating. We have chosen to base our data on the first 7 days after birth. On the other hand, Dr. Apgar, in her studies of respiratory distress, has used the first 28 days. I think there is little evidence that the respiratory distress syndrome extends beyond the first week. It would be helpful if we could all agree on a uniform period. Another matter that concerns me is the occasional report of rather high survival rates among infants under 1,000 grams. I have always felt that such good survival rates depended on the fact that the infants probably were weighed for the first time many hours after birth. All of our infants are weighed immediately after birth. Our survival rate among infants of 1,000 grams or less is practically zero. I am sure, however, that we could improve this if we waited 12 or 24 hours to take the initial weight. I think that, in order for comparisons to be made from one clinic to another, care should be taken that the small infants be weighed at a uniform period. Any delay in taking the birth weight should be reported.

We have not been able to make an accurate differential clinical diagnosis between pulmonary hyaline membranes and pneumonia or cerebral hemorrhage. Of course, if an infant dies during the first 2 or 3 days after birth without obvious congenital malformations, the chances are excellent that hyaline membranes will be found at autopsy. We have been fooled, however. For example, we have thought we were dealing with a typical hyaline membrane syndrome in an infant who died within the first 48 hours, but to our surprise found instead typical pneumonia at autopsy. Experts in radiology, like Dr. Caffey, say they cannot make this differential diagnosis with certainty on the basis of roentgen examinations. I get the impression that the radi-

ologists are correct about 80 to 85 per cent of the time, but we need a technique for making this diagnosis 100 per cent correct on clinical grounds. Our method of classifying infants according to the trend of their respiratory rates permits us to differentiate healthy babies from those with respiratory distress, but not to make a differential diagnosis between hyaline membranes, pneumonia, or cerebral hemorrhage.

DR. SMITH. Now we will ask Dr. Mary Crosse to discuss the same questions.

DR. CROSSE. Thank you very much. I am most relieved, Dr. Miller, that you have not been very definite about diagnosis because I am going to be still more indefinite. When I was asked yesterday whether I could say anything useful I said I thought I might perhaps make everything that is muddy water, muddier still! It is a very difficult subject. As regards making a definite diagnosis between hyaline membrane and other respiratory distress, I would like to admit here and now that I cannot. I commit myself in writing and I try to get my registrar to commit him or herself in writing and we are wrong more times than we are right, although from the statistics it should be the other way round if we pin our faith on hyaline membranes. That is a little bit depressing and personally I feel I cannot speak about a clinical diagnosis of "hyaline membranes" so I suppose I have to go on speaking about "respiratory distress." As regards respiratory distress, there are one or two things that I personally look upon as bad prognostic signs—I think that is what you want to know our opinions about. I hate this "crying" expiration—you know the sort of noise that they make. When I go into the premature unit and hear that, I say, "Good gracious, who is going to die in the next few hours?" That is one bad sign and then, of course, the prognosis depends on the birth weight.

I would like to stress the point made by Dr. Miller about weighing at birth and to say that I have never known immediate weighing to prejudice the chances of the child. It does not hurt a baby to lift it out of the portable carrier onto the scales before it is put into the incubator, and I think that it is very important to know the true birth weight of a baby from the point of view of prognosis. Again, I am sure that marked recession (i.e., retraction) has a bad prognosis. Personally, I find that our incidence (in each birth weight group) of hyaline membrane found post mortem is in inverse proportion to the rectal temperature of the babies when they are admitted. Eighty per cent of our babies are admitted from outside the hospital. I find that another bad prognostic sign is edema. Edema is found more frequently in babies with hyaline membranes than in babies without hyaline membranes. Apneic attacks, rising pulse rate, increasing respiration rate, and increasing recession are all bad signs. I feel that if a baby is in good condition at birth and starts to breathe immediately that is a very good sign. I am sure that the babies who develop respiratory disease are not, as they used to be described, "good at birth and then deteriorating." I do not believe that; I think they are usually in a poor condition from the beginning. As regards the time factor, we heave a sigh of relief at the end of 48 hours because our death rate at the end of that time is very low. Another thing that is a bad prognostic influence is birth asphyxia. We find that babies with a history of birth asphyxia have a higher incidence of hyaline membranes: antenatal complications and labor complications leading to asphyxia also result in a higher incidence of hyaline membranes. As regards grading of severity of the condition, I can speak only for respiratory distress and I can suggest only that Dr. Apgar's grading might be modified in some way and we could grade for the color (whether they need oxygen or not) and body temperature; and I think we might also grade edema and pulse rate. These are my preliminary remarks.

DR. SMITH. Dr. Benirschke, can the pathologist always make this diagnosis? If he cannot, it is going to be harder for the clinician.

DR. BENIRSCHKE. It is reassuring to hear people tonight stand up and speak of hyaline membrane as an entity; a few years ago, no one wanted to come straight out with this diagnosis. The difficulty of predicting clinically at the Boston Lying-in Hospital whether the autopsy will show cerebral hemorrhage, hyaline membrane disease, or pneumonia is impressive to me too. I do feel, however, that in infants who die before 2 days, one should be able to differentiate deaths from pneumonia, if one always looked at the placenta. It is most uncommon for any infant to die of pneumonia at 2 days with a normal placenta; in pneumonia at this age and weight, the placenta is usually inflamed.

I think the pathologists here will agree that hyaline membrane disease is definable pathologically. The membranes and the resorption atelectasis go along with a gross macroscopic appearance of the lung, hardly mimicked by anything else on the autopsy table. Only in the later stages, i.e., at 3, 4, or 5 days of age, when resolution of membranes by an inflammatory process takes place, is diagnosis more difficult. Hyaline membrane disease seems rarely associated with bronchopneumonia acquired in utero; if this does occur, differentiation can be made by the eosinophilic staining of the hyaline membranes versus the blue of the fibrin in bronchopneumonia. Finally, I think pathologists would agree that the almost invariable association of membranes with degenerated epithelial tissue at the junction of membranes with bronchial epithelium demands further attention. This is sometimes quite marked and always present.

DR. SMITH. Now let us have a general discussion, starting with the clinical diagnosis.

DR. BAAR. This was once thought of as a "vernix membrane" and assumed to be specific for the newborn, especially the premature. Actually, McCallum described hyaline membranes in an epidemic of influenza among young adults almost 50 years ago. We often see them in inflammatory exudates, as during the recent epidemic of Asiatic influenza. In newborn infants they appear as transudates with chemical properties of an exudate, without any cellular evidence of inflammation. Numerous factors contribute to their development. Hyaline membranes may be associated with an eosinophilic fluid or a fibrin-rich exudate which is only concentrated, but not necessarily in membranes, or one may see homogenous or granular eosinophilic material filling many alveoli with only few hyaline membranes. The clinical effects will be the same. As to an in vivo diagnosis of hyaline membranes, I say I cannot make a gross postmortem one, after postmortems on hundreds of premature newborns. I can only make it microscopically. I have reported the factor which predisposes the premature infants in a paper in the *Festschrift* for Frontali.[1] Premature newborns frequently have subcutaneous edema associated with hyaline membranes and associated with marked edema of the subarachnoid space. The subcutaneous edema fluid, easily accessible without contamination with blood, is obviously a transudate in the subcutaneous tissue, has an average protein content of 6.4 to 7 Gm. per cent, and an electrophoretic pattern like that of the blood serum, except that the albumin is as high as 80 per cent on the average. Thus, we have extravascular fluid with colloidal osmotic pressure so high that there is what I call the "reverse Starling mechanism." This is added to the vascular hydrodynamic pressures and persists as long as the characteristics of the transudate persist. Changes occur so quickly that we see the majority improve by the second day of life. So I believe the basal mechanism is exudation or transudation of protein-rich fluid into the alveoli after having passed the basal membrane, and that the degenerative changes in the epithelium start somewhat later. They are very common, but occasionally you see quite a continuous layer of epithelial cells with hyaline material between it and the mesenchymal part of the intra-alveolar sac. Although there may be many other factors, such as asphyxia neonatorum

of cerebral origin, besides this basal mechanism, I believe the main reason for the frequency of hyaline membrane in premature newborn infants (and the basis on which the clinician should attack the problem) is a difference of permeability.

DR. BURNARD. I wonder, however, if it would be profitable to consider not just prematures but all babies who are breathless, and see what they have in common, because full-term babies get into distress and full-term babies also, on occasion, do have hyaline membranes. The question I should like to ask Dr. Benirschke is whether he admits anoxia in the classification he gave today of causes of neonatal death as recognized post mortem.[2]

If you do include anoxia, as recognizable by postmortem features, perhaps you can then tie in the statement of Dr. Crosse that premature babies born with difficulty have a much worse prognosis. It may be, in fact, that the asphyxiated full-term baby is the one more likely to get into this kind of difficulty. Here is a sort of common meeting point. If we study all these babies from a clinical point of view, we may find something in common without being committed to a pathologic diagnosis, which, in fact, may not have any real relevance to the physician.

DR. BENIRSCHKE. I rarely make a final diagnosis of pure anoxia at autopsy, except in stillbirth (or immediately postnatal deaths) after abruptio placentae, or in monoamniotic twins where one may be entangled in the other's cord. Our classification for neonatal death has been relatively consistent during the last few years, so that in some 40 of the 100 or so babies who die neonatally we examine a year, there is a good hyaline membrane formation. There may often be other lesions such as cerebral hemorrhage or other minor things, but *primarily* atelectasis with membranes. In the miscellaneous group of our classification, there are a few babies of 600 to 700 grams' weight who died within ½ to 1 hour after birth. Had they lived, they might have developed hyaline membranes but since we cannot yet show membranes (though there is generally some atelectasis), a primary diagnosis of anoxia is made. I do not think it should be made in many autopsies after neonatal deaths.

DR. SMITH. This is difficult. I think we should stick to prematures, to reach any clinical diagnosis at all, but admit occasional occurrence in others. Obviously, the pathologists know what we are discussing better than we clinicians.

DR. GRUENWALD. I won't argue about terminology—let us call it hyaline membrane disease; there are sometimes lots of hyaline membranes, sometimes few, and sometimes none. In the premature it occurs as a characteristic form of atelectasis with distended respiratory bronchioles. Unless one wants to decide arbitrarily how many hyaline membranes are required for diagnosis, I think this entire spectrum should be included. The atelectasis, which is really what bothers the baby, should be the basis of microscopic diagnosis and fits the fairly characteristic gross appearance. But, as Dr. Avery can tell us, there are other methods from autopsy material which have taught us something new. Even if we have found out what the membranes are, we still know very little about the disease. We now know that these lungs have some peculiar properties, and that an extract of them will again have these peculiar properties. This suggests absence of a normally present substance from abnormal lungs, as Dr. Avery[3] mentioned in her paper. We now have something to look for and to study, from which we may be able to make a laboratory diagnosis of either this form of respiratory distress or perhaps of a wider group.

DR. JAMES. I would like to agree with Dr. Gruenwald that the hyaline membranes have tended to serve as so many red herrings. I do not think this condition should be a pathologic diagnosis but rather a clinical one. Respiratory distress is something we see in the baby. Excluding congenital anomalies, the great majority of infants who die in the first 3 or 4 days of life show extensive atelectasis. However, only about

half of these infants have hyaline membranes as well, their clinical course being similar to that of the ones who die without membranes. In this light it would seem that the term hyaline membrane disease is a misnomer, and we should call this condition by another name.

The study of Dr. Calkins and Dr. Miller stimulated us to compare the baby's condition at birth (Apgar score at 1 minute) with his subsequent clinical course (graded according to the Silverman retraction score). There was a highly significant correlation in 277 premature infants (less than 2,000 grams). This strongly suggests that premature infants who are vigorous at birth develop respiratory distress less frequently than those who are mildly to severely depressed. Of 110 infants who died following a symptomatic course of respiratory distress, 81 per cent were moderately to severely depressed (Apgar score 6 or less) while only 19 per cent were in the vigorous group (score 7 to 10). These clinical observations suggest that asphyxia plays a basic role in the respiratory distress syndrome. The premature infant may be only mildly asphyxiated when he is born, but through inability to ventilate adequately (from weakness of the chest wall and decreased pulmonary compliance) is unable to recover from this state and maintain normal acid-base balance. In our experience the only full-term infants who develop respiratory distress are those who are severely asphyxiated at birth (e.g., placenta previa).

DR. MILLER. We have just finished a study in which we correlated conditions in the first minute after birth with what happened subsequently to the infant: (1) We studied 500 consecutively born full-term infants whose mothers were delivered vaginally. The incidence of respiratory difficulty was so low in this group as to make it not worth our while to use either method of classification as a routine procedure in our nurseries. (2) We have studied 180 full-term infants born by cesarean section. There were 3 deaths and all 3 deaths occurred in the group of 33 infants who failed to breathe spontaneously in the first minute after birth. All 3 of these infants also were found to belong to our abnormal respiratory group III.[4] We feel that both of these methods of evaluation are helpful in the case of babies born by cesarean section and we do make this part of our routine in our nurseries. (3) We have studied over 600 consecutively born premature infants with birth weights from 1,000 to 2,500 grams. There were 32 deaths and the immediate type of assessment failed to predict 11 of these. In other words, there were 11 infants who breathed immediately after birth who subsequently died. On the other hand, all 32 infants who died were classified in our respiratory group III.

There is validity in Dr. Apgar's scoring method[5] but it is not 100 per cent. Dr. Apgar's statistics indicate that about 50 per cent of premature babies survive the first month in spite of low Apgar ratings of 4, 3, 2, 1, or 0. I would like to hear what Dr. Apgar has to say about this.

DR. APGAR. May I comment on some earlier discussion as well? Dr. Miller, you are absolutely right that it would be more valuable to have mortality statistics for one week rather than 28 days. Babies at the Sloane Hospital are all weighed in the delivery room; premature infants within the first 10 minutes of life. I wonder whether Dr. Benirschke suggested something quite important when he spoke of diagnosing potential infection from frozen sections of placentas after ruptured membranes rather than waiting until the baby died. As to the diagnosis of hyaline membrane disease, clinically or otherwise, I am a complete pessimist. I do not believe there is such an entity, and therefore it is hardly worth while to classify it. Respiratory distress has many factors. Whether these symptoms are from cardiac failure, metabolic disturbances, or inherent enzyme deficiencies, or whether the problem is one of transudate atelectasis or congestion of the lungs, I do not believe we know enough to classify the syndrome at present. But with further work and combined results we might do better. Dr. Miller,

I do not remember those figures on the premature infants, but I believe the death rate was worse than you mentioned in your 2,000 infants of less than 2,500 grams with scores of 4 and under.

DR. MILLER. Is this one minute assessment enough?

DR. APGAR. The combination of both is a good idea. I am sure that immediate assessment has a place. As to sustained respiration, 70 per cent of our infants are yelling and breathing in one minute, 90 per cent in 2 minutes, and about 94 per cent in about 2½ minutes. Those who take longer are really in a bad way. This happens to fit the scores at birth as well. Both Dr. Silverman's[6] method of scoring and your respiratory rate of scoring, with few exceptions, work quite well for follow-up. Observing chest, or xiphoid, retraction, expiratory grunt, dilation of the alae nasi (instead of the chin tug) in our prematures has indicated the prognosis well in all kinds of respiratory distress.

DR. MINKOWSKI. Surely there is more than just respiratory distress because newborn infants with many anatomic and physiologic conditions tend to react similarly. After 10 years I still make many diagnostic errors. In respiratory distress, not only hyaline membranes, pneumonia, and metabolic conditions, but also cerebral causes can give the same picture. Neurological examinations seem to give more accurate grading of clinical severity than others, for the brain is the first organ to suffer in respiratory distress. Instead of relying on any of the clinical signs directly related to respiration, in our clinical examinations, we look for two neurological signs: (1) abnormal tonus, which is very important, and (2) definite abnormalities of what we call the "primary automation." The severity of those signs gives us a more accurate prognosis than does the clinical respiratory picture alone.

DR. DESMOND. After three years of sitting with infants and observing distress, our group in Houston has now formulated a predictable sequence of clinical behavior which these infants show in two phases, cardiopulmonary and neurological. As for the pulmonary, at the lowest or more severe point, the infant has apnea. With improvement he goes from apnea to gasping, then to grunt and less labored respiration. At a point where the circulation seems to be improving, the infant develops a rapid regular respiration. After a variable period, he goes into irregular respiration, which again eases as the rate goes down and breathing approaches normal labile or periodic. Similarly, with the heart, at the lowest point there is bradycardia; improvement brings a regular and fixed heart rate, with sounds loud and clear. This usually accompanies the grunting phase. As the infant improves further, the heart rate briefly becomes quite rapid and then approaches normal or 120 to 140.

Neurologically the lowest phase is hypotonus; with improvement, tonus improves, becomes increased, and then returns to normal. Similarly, reflexes at the lowest point are absent, then improve, and become exaggerated before returning to normal. Gastrointestinal activity goes from ileus to hyperperistalsis to abdominal distention to normal. The lowest phase appears to be one of parasympathetic hyperactivity, with the infant quiet, hypotonic, inactive, and the pupils at mid-dilatation. As he improves, there is an abrupt change to sympathetic hyperactivity, with spontaneous movement, opening of the eyes, abdominal distention, hyperexcitability; at this period one often sees the first signs of dermatographia. So we feel that prognosis depends on which direction a baby is going in these sequences—up or down, and that, at the normal stage, the infant seems to have both parasympathetic and sympathetic activity together.

DR. CLAIREAUX. I have been rather foxed by the discussion of my fellow pathologists tonight. My friend Dr. Gruenwald suggests we call this hyaline membrane disease and adds that 50 per cent may not have a membrane at all. We have to be careful about this since radiologic examination seems to offer about 85 per cent cer-

tainty in diagnosis. If the pathologists can then say: "We have cases which seem to be among those you are discussing, but only half of ours have a membrane," then where are we getting with our diagnosis? I agree the atelectasis—an unusual distention of the respiratory bronchioles and ducts with a collapse of the distal parenchyma—is one of the difficulties of these infants. In some of these there is considerable added edema, and in most a hyaline membrane. Only about 30 per cent of our infants in that group would have no membranes.

Dr. Corner. All babies born in two maternity units under my care, or about 5,000 a year for 10 years, have been graded as to timing of first respiration, need for and amount of any kind of active resuscitation, color, muscle tone, and circulatory state. We have thus found that most of them who need any active resuscitation (intubation, gastric oxygen, etc.) are the more mature or full-term ones, rather than the very small or the very premature, most of whom breathe almost immediately and need very little active resuscitation. We have also been keeping detailed counts and charts of the respiratory rate every hour or every half-hour for 48 hours after birth on all the 500 or so premature babies a year. Our third set of clinical observations are rate of apex beat, presence of edema, presence of jaundice, type of respiration, alterations in chest shape, twitching, vomiting, regurgitation, and so on. We find that while many of the babies who subsequently develop hyaline membrane disease breathe immediately, all have some respiratory problems following the first breath after birth. Their breathing, once it starts, is never quite normal. Grunting, or a little cry, occurs in the most severe cases but not all. Particularly in babies with the hyaline membrane syndrome at postmortem, the respiratory rate rises within the first 2 hours, nearly always to 60 or more by the end of the second hour.

The apex beat does not alter once respiratory distress of any type is well established; heart rates of 130, 140 are recorded for some hours after the respiratory distress has become extremely severe. But by careful palpation, we have noticed that in the first hour the peripheral pulsations are extremely weak in babies who subsequently develop the severe and fatal types of respiratory distress. In fact the radial pulse has often been quite impalpable ½ hour after birth, while the apex beat is still counted at 140 per minute. This may be clinically helpful. At obstetric-pediatric-pathologic perinatal death conferences, these detailed clinical observations are to some extent correlated with postmortem findings. Though, like Dr. Crosse, we cannot predict the hyaline membrane syndrome accurately, I do feel that the baby who is never right from birth is very likely to have hyaline membranes at postmortem, whereas the baby who never has a rising respiration rate will not.

Dr. Reardon. I should like to add to that excellent discussion that we think muscle tone very important in differentiating the very ill babies; indeed, our obstetricians tell us at cesarean sections whether they think from the feel of the baby that he will be ill. Muscle tone can be poor without other obvious signs. Subnormal temperatures are also significant, and change in temperature from reasonably good toward subnormal suggests poor prognosis.

Dr. Miller. What kind of thermometer do you use? Let us get one that goes down to zero.

Dr. Reardon. Temperatures that are off the thermometer are definitely subnormal but should be measurable. The normal full-term infant's temperature will be up to 97° (on our Fahrenheit thermometers) in 24 hours and usually much sooner. Air-conditioning and exposure will influence this. The temperature of prematures will vary according to their size, and in some small ones is only 95 to 96° F. with the aid of environmental warmth. If one cannot get the temperature up to 95 or 96°, prognosis is poor. One can learn much by merely feeling the baby.

Dr. Miller. We must be careful here,

because under standard conditions of environment and humidity, our premature babies with temperatures of 90° F. may survive. Perhaps Dr. Crosse can define what a subnormal temperature is.

DR. CROSSE. Most of our babies come from many miles away. Their temperatures on admission often worry me. The incidence of hyaline membranes for all the prematures under 2,000 grams at birth is usually between 10 and 13 per cent of the admissions. But, in babies who come in with a rectal temperature below 92° F., the incidence goes up to 19 per cent, while babies with temperatures over 92° F. have the lowest incidence (if the temperature is above 98° F., the incidence is down to 5 per cent). This is not connected with birth weight; it happens in each birth group.

DR. BAAR. I fully agree with Dr. James that hyaline membrane disease is a misnomer. The term "respiratory distress syndrome" which implies what the clinician sees, and does not pretend to diagnose (since the pathologists can diagnose it only by the microscope), is preferable. But I do not agree that asphyxia is primary. Asphyxia is always secondary, either to cerebral, pulmonary, cardiac, or cardiopulmonary causes. In the vicious circle of these interconnected factors, we cannot decide even at the postmortem examinations which is the primary one in small prematures. In full-term babies, however, although histology is unreliable, if the succinate dehydrogenase activity of the myocardium is estimated we find it very low in myocardial insufficiency of whatever etiology. Actually, succinate dehydrogenase activity of all neonatal tissue including the myocardium is normally less than half the normal at a later age—and this may be a factor contributing to disorders causing the respiratory distress syndrome.[7]

Though in hyaline membrane disease the respiratory rate may increase in the first 2 hours after birth, I have never seen a newborn die in less than 2 hours (actually less than 6 hours) with hyaline membranes.

DR. GRUENWALD. In addition to pulmonary, cardiac, or cerebral factors, asphyxia may result from disturbances of the placenta or its circulation, and thus before the pulmonary, cardiac, or cerebral manifestations, which appear later. Dr. Claireaux, I didn't want to argue about terms—I still think that hyaline membranes are an "eosinophilic herring" as I have said for years—but the type of atelectasis results from the degree of maturity. A full-term baby may have hyaline membranes at autopsy, but without the peculiar form of atelectasis with distended bronchioles. We have to keep two things apart: (1) development of atelectasis and (presumably) respiratory distress, and (2) the special form of atelectasis in any premature infant who has atelectasis and dies within the first 2 days. After 48 hours the lungs of the premature begin to behave like more mature ones. I did not imply the name hyaline membrane disease should be maintained.

DR. SMITH. Are there 2 kinds of atelectasis in this disease, one peculiar to prematures and the other seen in term babies? Dr. Baar apparently agrees, but what about Drs. Benirschke, Driscoll, Craig, and Claireaux?

DR. BENIRSCHKE. Dr. Craig should discuss this. He not only demonstrated with Dr. Gitlin the nature of the membranes, but he has also studied the obstructive phenomena and atelectatic pattern in these babies. I do not think there are two patterns, but I do think this is a disease peculiar to the newborn. Membranes occur in other conditions, such as influenza, but without the typical absorption or resorption atelectasis so peculiar to the newborn.

DR. CRAIG. I agree with Dr. Benirschke about the nature of atelectasis, and that it is not particularly different in premature and term infants. Infants with hyaline membranes have an atelectasis quite unusual in any older individuals. I am less certain of prematures without membranes.

DR. DRISCOLL. I quite agree with Dr. Craig and Dr. Benirschke.

DR. BAAR. The peculiarity is from the anatomy. In a latex cast of the lung of an in-

fant of 10 months, one can distinguish individual parts of the bronchial tree; a cast of a newborn lung shows few and very small branches, so the peculiarity is specifically one of the newborn and not of the hyaline membranes.

DR. CLAIREAUX. I am afraid I had better say something because I started this, but I do not really believe there are two forms of atelectasis here. I think we are probably arguing at cross-purposes.

DR. DRORBAUGH. If we want to study something clinically which is identifiable pathologically, we must try to identify it before the baby dies. Realizing that our clinical diagnosis may be wrong, still, we do diagnose hyaline membrane disease as the disease we are studying. In doing so, one systematically records the same set of observations for each infant. We, like others, have recorded respiratory rate, cyanosis, and retraction, and have been impressed by the neurological manifestations. Even very early in the disease, babies with respiratory distress are not active, crying, or alert, but limp, hypotonic, and unresponsive. They very frequently present resuscitation problems in the delivery room. With us, they seem also to be neither the full-term babies nor the smallest prematures, but those who weigh between 3 and 5 pounds.

DR. COHEN. We all agree that these babies are in poor condition, and that function of the placenta may be very important here. In Buffalo, we found a significant number of cases of placenta previa and are suspicious of premature separation as a factor. We do not know how to diagnose inadequate placental function. Could the excellent experiments detailed at this Congress be turned around, and catheters put not toward the baby but toward the placenta?

DR. JAMES. I certainly agree with Dr. Cohen that we have little knowledge of how the placenta is functioning before and during labor. Placental dysfunction is one of the important factors contributing to birth asphyxia.

DR. SEGAL. I hope we may come closer to agreement on signs so that results of therapy when reported, can be compared. Could "recession" or "retraction" be objectively and quantitatively described? Dr. Desmond made a most important point about the timing of signs. How did they start? Are retraction, grunting, poor tone, and so on, getting worse or improving? Could this meeting emerge with a single system of grading babies as to both degree and time, on which to evaluate therapeusis?

DR. TIZARD. We should at least agree about attempting to measure temperature accurately. Thermometers registering down to 75° F. are obtainable and should be used. Accurate measurement of recession [chest retraction] is difficult, but from the clinical standpoint the degree of recession seems to me to correlate very poorly with severity of the disease. Since it expresses both the degree of obstruction and the vigor of the baby's response, we think the most obvious recession by no means has the worst prognosis.

Then, in the guessing game of diagnosis, one should be greatly influenced by the time that the baby has lived. Hyaline membrane is less likely at autopsy of small prematures a few hours after birth, than when the distress has continued during many hours—I am not going to put a figure on it. Dr. Claireaux will remember a death at one hour with hyaline membrane formation, but that is exceptional. Dr. Benirschke mentioned the difficulty of clinical decision between hyaline membrane or respiratory distress syndrome and intracranial hemorrhage. I thought subdural hemorrhage meant injury of some kind but intraventricular hemorrhage was an accompaniment and frequently the terminal event in the respiratory distress syndrome. Attempts to distinguish between death from the respiratory distress syndrome and that from intracranial hemorrhage are mistaken because so many infants with respiratory distress (with and without hyaline membrane disease) are found to have an intraventricular hemorrhage at postmortem.

DR. MILLER. I like the direction in which

the discussion is going at the present time. The clinicians here are now asking the important question: How does one quantitate the various signs that everybody has been talking about here? The word "recession" has been used as though it was clear exactly what is meant by it. I do not know whether the sternum is or is not retracted in what I call "see-saw" breathing, where the chest goes down as the abdomen goes out. I do not know if "see-saw" breathing has anything to do with obstruction, recession, or retraction. It is so normal in older infants that I am dubious as to its significance in the first few hours. What we would call recession, and I am not sure that other people mean the same thing, is pulling inward of the lower portion of the thoracic cage and lower sternum as the upper chest and the abdomen are expanding outward. I wish we could quantitate "tone," and the same is true of our vague descriptions of edema and retraction.

DR. COOK. Severity can be graded by groups selected to do so. As to retraction, the sickest baby, who has stopped breathing entirely, has no retraction and with gradual weakening retraction becomes less and less, so retraction per se may be a poor method of grading severity. I do not agree with the clinicians' and pathologists' implication that we are not talking about anything specific and therefore cannot define it. I think we are talking about a definite entity, and I would like to list some facts about what we might call the respiratory distress syndrome, hyaline membrane disease or syndrome, or even "resorption atelectasis." Dr. Avery has made such a table, and I hope she will change this if she wishes (Table I). Can we not all agree on these features? Under *clinical,* certainly the "history of prematurity" is agreed on as important. A history of intrauterine distress, also important, has not been mentioned tonight. Often one finds there was similar distress in other siblings; therefore, I would include a family history.

There are obvious *physical* findings: low birth weight (naturally with prematurity) and tachypnea, most frequently starting at birth. Retraction, however graded, is not specific, but almost always a feature of this as of most conditions causing respiratory distress. If the distress is severe, cyanosis is present. Any sick infant has a tendency to low temperature and, therefore, I feel that this is only a nonspecific sign of illness, as hypotonia may be. How can one define a respiratory disease in terms of the amount of hypotonia that it produces?

Certainly *laboratory findings,* such as changes in pH and changes in carbon dioxide, may be helpful but not very specific. Absence of placental findings is of value; as Dr. Benirschke has pointed out, without placental inflammation, pneumonia as a cause of respiratory distress is unlikely. X-ray is not an absolute diagnostic aid, but is helpful, especially in conjunction with other findings.

Consistent, though not absolutely diagnostic, *physiologic findings* contribute to the

Table I. The respiratory distress syndrome

Clinical.	
History of prematurity	
History of intrauterine distress	
Family history of respiratory distress in other siblings	
Diabetes	
Physical.	
Birth weight of prematures	
Increased respiratory rate	
Retraction	
Cyanosis	
Subnormal temperature	} will occur in any sick infant
Hypotonia	
Laboratory.	
pH, fall	
pCO_2, increase	
Placenta, absence of findings	
X-ray of chest, helpful	
Pathologic.	
Atelectasis	
Hyaline membranes	
Edema	
Physiologic measurements.	
Functional residual capacity, decreased	
Lung compliance, markedly decreased	
Blood pressure, fall	
Biochemical measurements.	
Surface tension changes	
Absence of fibrinolytic activity in lungs	

picture. Dr. Karlberg has described decreased functional residual capacity. There tends to be a marked decrease in lung compliance, not only in life, but also demonstrated by Dr. Avery at autopsy. The consistent fall in blood pressure described by Dr. Neligan and others might be either a primary or a secondary factor. Finally, the most interesting *biochemical changes* are the ones we know least about. Dr. Avery's[3] data on surface tension changes seem to be important and consistent, and there is also the absence of fibrinolytic activity in the lung tissue itself, described by Dr. Lieberman.[8] In view of all these things, I hope we will end this meeting by deciding that we are talking about an entity with some definable characteristics.

DR. SMITH. Thank you. You can also include maternal diabetes.

DR. BENIRSCHKE. May I interrupt to set the record straight with Dr. Tizard? I believe that premature infants die *from* subdural hemorrhage, but they die *with* intracranial hemorrhage. I think, with you, that the intracranial hemorrhage is secondary to some respiratory or other asphyxial syndromes.

DR. USHER. I would agree with Dr. Cook that we are dealing with a distinct disease entity which has a specific clinical picture. It is not simply a wastebasket category for undiagnosable respiratory difficulty in the newborn period.

I would also add that it appears that this disease, unlike retrolental fibroplasia, has probably always been with us in the same frequency as today and that it is not therefore caused by recently introduced therapeutic techniques. This last statement I base on an analysis of the mortality rates reported by Ylppö for 700 premature infants. These infants, as reported before 1920, had exactly the same mortality rate for each weight group during the first 5 days of life as the best hospitals are reporting today. Since it is generally agreed that more than one half of these early deaths of premature infants are today a result of the respiratory distress syndrome, we must assume the syndrome was as prevalent in Ylppö's nurseries as it is in ours today, and that it carried a similar mortality rate.

I would now like to present some of my findings based on almost continuous clinical observation of 100 premature infants who comprised three equal groups: healthy infants, those with the respiratory distress syndrome who survived, and those who died. I found that the specific features of the disease were apparent during the first hours of life and consisted of chest retraction, expiratory grunting, and decreased air entry on auscultation. Although some healthy premature infants had these signs at birth, the signs were always mild and quickly disappeared within the first 3 hours of life. In distressed infants, on the other hand, the signs were often severe and always persisted at least 6 hours and usually became increasingly severe during this time. It was, therefore, sometimes necessary to examine infants repeatedly during the first 3 hours of life to establish the diagnosis with certainty. Using these diagnostic criteria, I found that the syndrome appeared in 14 per cent of liveborn premature infants, with the highest incidence in the lowest weight groups. The mortality rate in affected cases was 55 per cent, and the disease was the cause of 52 per cent of the deaths of infants who weighed 1,000 to 2,500 grams.

The respiratory rates were normal in survivors and below normal in fatal cases during the first hour of life. The tendency which Miller has described for the respiratory rate to rise in distressed and not in healthy infants was noted in our group, although a rising respiratory rate was also found in 20 per cent of the normal infants, and a stable or falling rate in 20 per cent of the distressed ones. The pulse rate and liver size were usually normal in distressed infants, although all 5 of the infants who had hepatomegaly were distressed and died.

Peripheral soft pitting edema of the backs of the hands and feet was noted in 85 per cent of the distressed infants and in only 10 per cent of the healthy infants, and this

10 per cent all had early mild respiratory distress and probably were borderline cases. In other words, it seemed the edema formation was not a result of prematurity (none of the 15 healthy infants below 1,700 grams developed it) but was caused by the respiratory distress syndrome. It developed 12 to 24 hours after birth in most cases, and usually disappeared during the third day of life.

Fine moist pulmonary râles typical of pulmonary edema were heard in half of the surviving infants and three fourths of the infants with fatal distress between 12 and 48 hours of age. Distressed infants were typically flaccid and inactive, especially between 12 and 48 hours of age; increasing activity and responsiveness were usually the first signs of recovery in survivors. Dr. Desmond mentioned that distressed infants could be irritable. I have found this irritability to be striking—infants with the syndrome often hyperreacted to the slightest touch or even to a bright light. Definite cyanosis which could not be corrected with increased environmental oxygen was a poor prognostic sign.

DR. GAIRDNER. Dr. Usher said exactly what I wanted to say. Pathologically, what we are talking about is a resorption atelectasis. I think we all agree that hyaline membrane is neither here nor there. Groaning or moaning is so specific that I wish Dr. James, Dr. Karlberg, or other students of physiology could tell us in physiologic terms what moaning really is. I would repeat that weak air-entry and fine râles on auscultation are highly characteristic. With reference to edema, so many babies appear to be born with little thin limbs which enlarge in an hour or two that we tried to measure this by simply encircling the leg very carefully with a thread and then measuring the thread. To our surprise, we found that the clinical appearance was illusory and that, if one measures these legs, they actually are shrinking. I think we must be very careful about the appearance of a shiny skin which is not actually swollen.

DR. WEINTRAUB. Is the edema Dr. Usher describes pitting, or "tight sclerematous" like the apparent tightening of the skin over the face after about 18 to 24 hours? Such tight sclerematous skin also goes with episodes of apnea and one feels that the infant looks as though he might have a cerebral hemorrhage. At autopsy there are no hyaline membranes.

DR. USHER. The peripheral edema I described is soft and easily pittable and is not sclerema. Sclerema in my experience is rarely seen in premature infants who do not have the respiratory distress syndrome, and is always preceded in distressed cases by the soft pitting edema which I have mentioned. It seems to result from a hardening of pre-existing soft pitting edema.

As to the grunt or moan, I have found it the most typical sign of the syndrome. Three infants who were grunting also had apneic spells and required endotracheal intubation and resuscitation to treat the apnea. With the endotracheal tube in place and the infant breathing spontaneously, grunting disappeared, which suggested that the grunt must come from the glottis and not from bronchial or bronchiolar obstruction. Does this concept agree with the feeelings of others here?

DR. SMITH. The hands indicate general belief that the grunt is made by the larynx, but because of trouble down below. Dr. Karlberg, what do pressure-volume loops indicate?

DR. KARLBERG. May I say something first about hyaline membranes? During my year in Boston in 1952-1953, I first appreciated this clinical entity, and when I returned to Sweden I began to look for the condition as it was quite clear to me that it was something one should differentiate. I found myself a very bad clinician, often unable to differentiate between cases of hyaline membrane and those of atelectasis of other kinds. As a matter of fact, I have felt that the incidence of hyaline membranes in Sweden is lower than here. I am disappointed that little has been said about x-ray examination today, for I do feel that it is a useful tool in the evaluation of respiratory distress. One

can clearly see in pressure-volume tracings that these infants are grunting. But it is not easy to describe the pattern, and I must admit that at present we have stopped working on it in our laboratory.

DR. JAMES. I think that accurate clinical observations during labor and immediately after delivery offer a valuable approach to diagnosis. In this regard, the observations of Dr. Desmond and Dr. Usher are a most important contribution. One sign which has received little more than passing attention is the expiratory grunt. It is likely to be reflex in origin but the exact mechanism of its production is not known. It is seen in pneumonia and in pulmonary edema. Theoretically it supposedly increases the intra-alveolar pressure during a prolonged expiration, reducing a tendency toward transudation from congested capillaries.

DR. SMITH. It occurs in some babies with intracranial hemorrhage without any respiratory distress and I believe is related to some central nervous system mechanism.

DR. MCKAY. We watch our babies carefully from birth and agree that the symptoms start then. But we have to provide criteria which can be used by people who (we hope) are less expert than we. These should include the x-ray. Not just the typical radiologic appearance of hyaline membrane disease, but the exclusion of pulmonary disease. I have missed conditions like eventration of the diaphragm, diaphragmatic hernia, and paralysis of the diaphragm by not taking an x-ray of a newborn infant.

DR. SMITH. Let us try to reach some conclusions. First, should what we are talking about be renamed or given an older name than the hyaline membrane disease? Whatever we decide, the world has just begun speaking of hyaline membrane disease, and is apt to continue; but if we think we can make the world change, I would be willing to move that this be called the "respiratory distress syndrome of newborn infants." If that is seconded, then we can have more discussion.

DR. RUDOLPH. I second it.

DR. SMITH. Does anyone want to suggest other possibilities or that we call the whole thing off?

DR. USHER. Should we restrict the name of this disease to the premature infant group who comprise 90 per cent of our cases of the respiratory distress syndrome, and regard the exceptional full-term case as well as the distressed infants of diabetic mothers as special separate categories?

DR. GRUENWALD. Some people think there is a difference between the process in term and in premature infants. If that is true, both names should be used.

DR. SMITH. As elsewhere in medicine, we are still fallible. I hope the term would mean that this is *clinically* "the respiratory distress syndrome" and not, as far as we can tell, pneumonia, pulmonary hemorrhage, or heart failure, or it would be so diagnosed. Restrictions to prematures may be left to the man reporting cases or writing a paper; he may describe the respiratory distress syndrome in a thousand babies, but he should tell how many were prematures.

DR. CLIFFORD. I expected Dr. Smith to congratulate me in holding off this long. I have objected from the very beginning to calling the condition hyaline membrane disease. What we are talking about now would be *idiopathic* respiratory distress syndrome—of unknown etiology. I find much in common in this discussion and the earlier ones when we first recognized that there was no such thing as hemorrhagic disease as a group. If we as clinicians would recognize that we are describing to the best of our present ability the etiology of this disease as determined by history, clinical observations, etc., we may say *respiratory distress syndrome, probably pneumonia,* or *probably intracranial hemorrhage,* or *idiopathic (hyaline membrane?),* etc., and then obtain a detailed pathologic examination. Unfortunately, some laboratories may see 2 or 3 little areas of hyaline membrane and call it hyaline membrane disease without checking much further. To me this discussion tonight is very encouraging, because the question of there being a hyaline membrane disease per se has bothered me so much

and I would prefer to call this respiratory distress syndrome of idiopathic origin. If we get together the most detailed clinical and laboratory observations, and correlate them with the pathologic findings, we may be on the verge of elucidating this whole field.

DR. SMITH. Thank you very much Dr. Clifford. Are there other comments at this point?

DR. MILLER. Do I understand that you would like to have this term "respiratory distress syndrome" limited to those cases that you thought had hyaline membranes?

DR. SMITH. I think Dr. Clifford's term *idiopathic respiratory distress* is good. This suggests that you are quite convinced there is no pneumonia or such other cause. The diagnosis may not be a narrow label but it is not a wastebasket either.

A SPEAKER. Is this the respiratory distress syndrome whether or not hyaline membranes are present?

DR. SMITH. The group seems to believe that though this syndrome usually includes them, one may not always find membranes.

DR. COOK. Do the pathologists think the term atelectasis should be included?

DR. BAAR. No, I think that it should be called respiratory distress syndrome.

DR. BENIRSCHKE. For a clinical term, I would leave "atelectasis" out.

DR. GRUENWALD. This is one difference between premature and full-term infants. In prematures (with this syndrome) you will practically always find severe atelectasis with distended bronchioles; in term infants, only a poorly aerated lung which in the strict pathologic sense may not be atelectatic. I do not think atelectasis should be in the name, but we should remember these differences in the condition in the full-term or the premature infant pathologically, and, I suppose, also clinically.

DR. MCKAY. I am opposed to this broad term "respiratory distress syndrome," for something which does not indicate merely respiratory distress in the newborn infant. As all who use this term are not as sophisticated as those here, they may well classify *all* patients with respiratory distress in the newborn period in this group without differentiating among them.

DR. SMITH. "Idiopathic respiratory distress syndrome," means that any other form of respiratory distress is ruled out.

DR. MILLER. I agree that using the term "idiopathic" might be the answer, but I would not like to see it remain just respiratory distress syndrome.

DR. CLIFFORD. A meeting like this can have a great influence. I was at one arranged by Dr. Julius Hess, which voted to recommend that 2,500 grams be used as a definition of prematurity and that all results should be given in the 500 gram groups. All the literature now says that this is the recommendation of the American Academy of Pediatrics—but they had nothing to do with it. It was just a group such as this, sitting around a table.

DR. USHER. If people publishing articles on the disease adopted the term "idiopathic respiratory distress of the newborn," the name would stick, no matter what the official recommendation was.

DR. KAY. I do think we are making progress but the neurological aspects are going to mean so much in future evaluations that I hate to see this name applied at the present time.

DR. SMITH. Does anyone want to discuss names any further? I do not think we need to take ourselves too seriously. Does anyone want to call it hyaline membrane syndrome?

DR. GAIRDNER. I would suggest rather using the term "pulmonary syndrome."

DR. CRAIG. I think it would be foolish to discard a term that is widely recognized, and so I would suggest calling it hyaline membrane syndrome, and not hyaline membrane disease.

DR. BAAR. Then you will have to have the term hyaline membrane syndrome with or without hyaline membranes.

DR. SMITH. If we have a good idea it will stick, if we haven't, it will be hyaline membrane disease. Are you willing to vote semi-officially on this?

How many are really in favor of advising that this be called:

Idiopathic respiratory distress of the newborn	15 votes
Pulmonary syndrome of the newborn	4 votes
Hyaline membrane syndrome	3 votes

Having gone only this far, it seems most unlikely that we can classify degrees of severity; I do not like to propose beginning such a discussion so late unless some one thinks a classification is feasible. In describing cases, one might at least include as many of the facts as Dr. Cook has listed (Table I), particularly neurological manifestations.

DR. CLIFFORD. There is now available a printed "newborn sheet" or standard examination form, with specific coding for IBM, prepared for the Cooperative Study. This may be of value in defining this syndrome by data which would make all comparable.

DR. SMITH. It would be excellent to have everyone collecting standard data, but for the neurological examinations there seems to be as yet incomplete agreement, in various parts of the world, as to record forms. Those in our country are probably set and established. From the thousands of babies to be followed in 15 hospitals in the Cooperative Study, this information will be obtained. I hope others will follow the same form, but do not wish to restrict people in other countries. Can we discuss anything further about the criteria of severity?

DR. SEGAL. Since the clinical picture is established in the first 1 or 2 hours after birth, should we not study this period closely?

DR. SMITH. There has been some disagreement as to whether these babies are or are not all right from birth. Of course, there are very mild grades of the idiopathic respiratory distress syndrome of the newborn; we cannot be sure some even have the disease. But how many believe all definite cases are observably abnormal from birth. *(All)* Is anyone brave enough to differ?

DR. SEGAL. A number of babies who have *some* grunting at the beginning are perfectly fine afterward, and there are *some* who appear normal at birth and do go on to die of hyaline membranes.

DR. SMITH. These things do make it difficult to know at 2 hours that an infant has respiratory distress and therefore can be treated early, or at 12 hours that he recovered because of the treatment.

DR. MINKOWSKI. Sometimes it stops and recurs.

DR. SMITH. Yes. Does anyone think that with present knowledge any statement of severity or prognosis can be given within the first 2 or 3 hours after birth? Most of us can identify the baby who is moribund at 3 to 4 hours, but the one looking fairly well at one hour who may be moribund 6 hours later unless treatment has been successful is the one we need to recognize.

DR. USHER. As well as performing controlled series to evaluate new forms of therapy, we should also report the effect of such new therapy on the over-all mortality rates for each weight group of premature infants in our hospitals. Since this disease is the cause of at least one half of premature infant deaths, any successful therapy should be expected to lower the seemingly unchangeable mortality rates which are standard at all major hospitals.

DR. SMITH. I agree. If you are willing to break off officially, I think we might have a motion for adjournment before midnight. Thank you all for coming. The meeting is adjourned.

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TROPICAL PEDIATRICS

The pattern of malnutrition in early childhood in southern Trinidad

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TRINIDAD, one of the 2 largest tropical islands making up the Federation of the West Indies, lies off the Venezuelan coast, and its very cosmopolitan population was about three-quarters of a million at the last census in 1955. The two main ethnic groups consist of those of African descent, who comprise the majority, and so-called East Indians (approximately 36 per cent) who are mostly third or fourth descendants of indentured labor coming originally from the Indian subcontinent, especially from the sugar-cane growing states of Bihar and Orissa.

In recent years Trinidad has become considerably more prosperous than the majority of the Caribbean islands. The estimated nation income per person has risen by 53.6 per cent between 1951 and 1959, as a result largely of the expansion of the oil fields and refineries, which are the source of approximately one-third of the country's fiscal revenue and directly support about 2 per cent of the total population (including both employees and their families). In addition, the island produces sugar with its by-products—rum, molasses, and bagasse; cocoa and citrus as cash crops, while the well-known pitch lake near La Brea forms an almost inexhaustible supply of asphalt. Over-all minimum wages have been improved by suitable legislation.

Road communications are excellent and cover the island. Each village has a small shop at which a variety of milk preparations are available, including relatively inexpensive brands of dried skimmed milk. Although the illiteracy rate is high (74 per cent), this is decreasing rapidly as about 90 per cent of the school-age population are in fact attend-

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ing school. Radio rediffusion is widespread, reaching the smallest villages.

The age structure of the island population shows the high proportion of children characteristic of most tropical regions, some 42 per cent of the total being below 15 years of age. However, despite a high illegitimacy rate of almost 50 per cent, there is good statistical evidence of improving health of the community, as indicated, for example, by a life expectancy at birth which has increased by 60 per cent since 1901, and an infant mortality rate that has improved from 162.3 per 1,000 live births in 1901 to 56.5 by 1957.

Despite these improvements, however, a recent report by Symonds[1] has shown that what has been termed protein-calorie malnutrition[2] is an important cause of admission and of mortality in the pediatric unit of the San Fernando General Hospital in southern Trinidad and that, in complete contrast to the usual main incidence between 1 and 3 years of age found in most tropical countries, the majority of affected children are under 1 year.[1]

SURVEY

Our study was based on San Fernando, the main town of southern Trinidad, which has a population of about 37,000, and on the surrounding County of Victoria, which contains approximately an additional 124,000 persons.

Hospital. This part of the investigation consisted principally of the analysis of case records, both of children admitted with a primary diagnosis of malnutrition, including kwashiorkor, and of those presenting with severe diarrhea in the first 2 years of life. In-patients in these 2 categories during the survey period were examined clinically. In addition, the numbers of children admitted yearly with these 2 diagnoses was tabulated, and their geographical distribution was plotted on transparent acetate correlation maps for the past 3 years.

Community. The major part of the survey was concerned with the field investigation of childhood malnutrition as it appeared in the actual community. Fifteen representative, but randomly selected, villages in different parts of the County and 2 slum areas adjacent to San Fernando were visited. In each case the public health visitor familiar with the district collected, as far as possible, the complete child population aged between birth and 4 years. Enquiry was also made of each mother as to whether any of her children was in the hospital.

Clinical examination consisted of recording: (1) the apparent ethnic group (usually predominantly African or Indian), (2) certain syndromes, (3) arm measurement (as detailed later), (4) certain simple signs considered to be of value as possible "nutritional indicators" of protein-calorie malnutrition,[3] and (5) some more definite and easily identifiable stigmas usually regarded as being often associated with certain vitamin deficiencies, (6) weight.

Syndromes. The following syndromes[2] were noted, when present: (1) kwashiorkor, (2) incomplete, mild kwashiorkor, (3) nutritional marasmus, (4) nutritional dwarfing, and (5) F. A. syndrome, in which the child was considered by crude inspection to be fat, flabby, and anemic with hypotonic muscles.

Arm measurements. These were made on the left arm with the elbow flexed to a right angle with the child seated on the mother's knee. The mid-upper arm circumference was recorded with a tape measure and skin folds were measured, using standard pressure Harpenden callipers,[4] anteriorly over the middle of the belly of the biceps and posteriorly over the mid-triceps.

Nutritional indicators. The principal clinical nutritional indicators employed in the present survey were those considered to have possible relevance to protein-calorie malnutrition,[3] and were based on those made use of in a recent field study in Haiti[5]: (1) edema, unequivocal pretibial pitting produced by "moderate" pressure for 3 seconds with a forefinger; (2) hypochromotrichia, any lightening of the color of the hair, affecting the whole scalp to more than half the hair length; (3) easy pluckability of the

hair, ability to detach some 20 hairs from the crown of the head easily and painlessly by pulling a clump of hair with "moderate" firmness; (4) low arm circumference and (5) low body weight.

A variety of more ill-defined minor signs, such as elasticity of the skin and excess tissue of the conjunctiva, as sometimes employed in field nutrition surveys,[6] were not included as it was felt that (a) because of difficulty of definition these features are of little value for comparison from one survey to another since they depend too much on subjective interpretation by individual examiners, and (b) that it was more justifiable to examine a greater number with a simpler "problem-centered" schedule, rather than to obtain a smaller amount of information of rather doubtful interpretation.

RESULTS

Hospital.

Malnutrition admissions. During 1958, 70 children with a primary diagnosis of malnutrition were admitted to the pediatric unit at San Fernando General Hospital, which deals with children up to 10 years of age. Analysis by age showed that, while no child with severe malnutrition was older than 3 years, only 10 (14 per cent) were within the "classical" 1 to 3 year period. The majority (60 children or 86 per cent) were aged between 1 and 12 months, and the main emphasis was in the second, third, and fourth months of life (27 children or 39 per cent). Ethnically, two-thirds of the children were East Indian, probably only reflecting the local population distribution in South Trinidad.

All 70 children were severely malnourished. A diagnosis of kwashiorkor was made in 18, of whom 15 (83 per cent) were below 1 year of age. The mortality rate for these 15 cases of infantile kwashiorkor was 47 per cent; 6 of the 7 deaths were in 2- to 4-month-old babies.

The remaining 52 children were classifiable as having other forms of protein-calorie malnutrition,[2] principally nutritional marasmus and other less clear-cut syndromes. No children were admitted with keratomalacia, infantile scurvy, or rickets during this period. Ariboflavinosis was seen only in association with protein-calorie malnutrition.

Dietary histories were available for 14 of the 15 cases of infantile kwashiorkor, and in all of them breast feeding had been what may be termed "nutritionally unsatisfactory." Thus, in 3 (21 per cent), breast feeding had not been initiated at all; in 3 (21 per cent), the breast had only been given intermittently, that is 2 or three times daily; and, in the remainder (8 children or 57 per cent), lactation had stopped prematurely, that is at least 2 months prior to the onset of illness. In all instances, infant feeding had consisted principally of mainly carbohydrate gruels and paps, such as sago, wheat flour or, more usually, arrowroot (86 per cent), sometimes associated with very small quantities of overdilute milk, usually one of a variety of dried products or occasionally a sweetened condensed preparation.

Of the total admissions with protein-calorie malnutrition, dietary details were available in 60, and of these 19 (32 per cent) of the mothers had not initiated breast feeding at all.

In the group of 18 children of all ages with kwashiorkor, there was a history suggestive of antecedent bronchopneumonia in 5 (26 per cent) and of marked diarrhea in 3 (18 per cent). By contrast, in the larger group composed of those of nutritional marasmus (Fig. 1) and other non-kwashiorkor protein-calorie syndromes, significantly severe diarrhea appeared to have been a precipitating or conditioning factor in 25 (48 per cent), while only 2 (1 per cent) were associated with probable bronchopneumonia.

Infantile kwashiorkor. As infantile kwashiorkor does not seem to have been observed as a common entity outside Trinidad, the clinical picture, already described by Symonds is worth restressing.[1, 8] In brief, the main features by which the syndrome in infants appears to vary from the more usual picture found in the toddler age group are: (I) the extremely marked subcutaneous fat,

Fig. 1. Nutritional marasmus. East Indian boy, aged 3 months, showing gross emaciation involving both muscles and subcutaneous fat. History: never breast-fed, dried milk 'formula in unknown amounts, diarrhea for 1 month prior to admission.

especially of the cheeks, producing a striking "wax-doll" face (Figs. 2*A* and 2*B*), (II) marked hepatomegaly, often down to the level of the umbilicus (Fig. 2*B*), (III) the uncommonness both of the "flaky-paint" dermatosis and of associated avitaminoses (Fig. 3), and (IV) the absence of significant hair changes, especially hypochromotrichia.

Diarrhea. In 1958, 493 children aged 2 years or less were admitted with a primary diagnosis of severe diarrhea, often requiring parenteral fluids; during the same period there were only 26 admissions of older children with diarrhea. From January to the end of May, 1958, 121 children of 2 years of age or less had been admitted with a primary diagnosis of severe diarrhea, and of these 21 (17 per cent) had died.

Bacteriologic examination of the stools was not available, and, although information on the case records was not sufficient to assess the precise nutritional status of these children on admission, the majority were malnourished, a considerable number being classifiable as marasmic. Analysis of these 121 cases of diarrhea by age and mortality showed that 69 per cent occurred in the first 6 months of life. (Table I).

Feeding histories were available in 69 of the 83 affected babies of less than 6 months, and of these 64 (93 per cent) were receiving what under present-day circumstances in Trinidad may be termed "bacteriologically dangerous" infant feeding. In 25 (36) per cent), breast feeding had not been initiated; in 27 (39 per cent), breast feeding had been stopped at least 2 weeks before the onset of diarrhea; and in 12 (18 per cent), breast feeding was only partial, that is, given 2 or 3 times daily, with supplementary foods, mainly dilute or carbohydrate gruels.

Hospital incidence of malnutrition and diarrhea. Although by no means statistically representative, a rough gauge of the incidence of severe forms of childhood malnutrition and diarrhea in southern Trinidad may be obtained by calculating the proportion of the total pediatric admissions in these categories during the past 3 years (Table II).

Community incidence.

Syndromes. The 4 more obviously identifiable syndromes of protein-calorie malnutrition were seen only rarely (Table III), whereas, by contrast, about 3 per cent of East Indian children aged between 9 months and 2 years were considered by inspection to be too fat, flabby, and anemic. Only 2 children with probable infantile scurvy were seen, aged 14 and 25 months; no clinical rickets was observed.

Nutritional indicators of protein-calorie malnutrition. The prevalence in the community of protein-calorie malnutrition can be expressed in terms of various "nutritional indices," that is the percentage showing a cer-

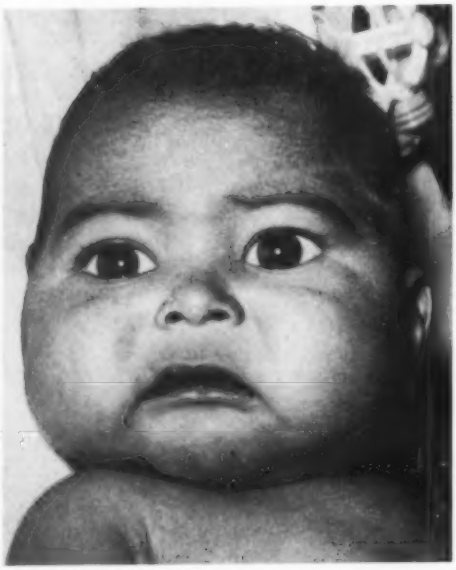

Fig. 2A. Typical infantile kwashiorkor. East Indian boy, aged 4 months, showing marked "wax-doll" face. History: breast-fed for only 1 month, followed by very small amounts dried milk formula and arrowroot.

tain "nutritional indicator" (Table III). These did not reveal much abnormality, and, in fact, are probably too crude for the situation in present-day Trinidad.

Weight deviation, arm circumference, and standards. Two problems are usually present when anthropometric data obtained from tropical children are evaluated: first, the question of accuracy in relation to age estimation (which is not a difficulty in Trinidad as birth certificates are usual), and, second, a customary absence of local standards.

In the present study, 2 weight standards were employed. First, an external one, taken from Nelson's *Textbook of Pediatrics,* which is based on findings in American Caucasian children, but which is widely employed and permits comparability from one region of the world to another.[9] Second, standards were sought based on measurement of local children of both African and East Indian descent. None were readily available, but average weight levels of these 2 groups were worked out from carefully selected child welfare records of apparently healthy, well-fed children. They were, however, available only up to the age of 2 years.*

Weight deviation below both these 2 standards was expressed by using the Gómez weight classification into 3 degrees[10] (Table III).

Local standards for the average upper arm circumference were impossible to obtain for either ethnic group in the time available. However, for Trinidadian children of African descent, a standard was employed that had been prepared in Jamaica in a similar ethnic group.† "Low arm circumference" was defined as 80 per cent or less of the average. The low arm circumference index for African preschool children only is shown in Table III.

Miscellaneous nutritional indicators. The prevalence of Bitôt's spots, follicular hyperkeratosis, and angular stomatitis is shown in Table III.

Infant feeding (Table IV). In the first 3 months, breast feeding was usually successful, although in 10 per cent of East Indian mothers failure had already occurred. However, at the same time, in one-half to two-thirds, feedings with various preparations of cow's milk were also employed. These were usually very haphazardly prepared formulas made up from dried powdered milks and given at odd intervals. Carbohydrate gruels were sometimes used, most usually arrowroot. Bush teas, as drunk in Jamaica[14] and elsewhere, were occasionally introduced this early, and may include a wide variety of herbal infusions.

During the 4 to 6 month period, there was a decline in complete breast feeding. 24 per cent of mothers in both ethnic groups having stopped. Occasional breast feeding

*Kindly supplied by Dr. Elizabeth Quamina, Assistant Medical Officer of Health, Victoria.

†Kindly supplied by Dr. Verity Wills, Tropical Metabolism Research Unit, U.C.W.I., Jamaica.

(about 2 feedings during the day with an occasional one at night) was being employed by a quarter of East Indian mothers, probably because of the necessity of their working during the day in the cane fields. Bottle feeding increased to 80 to 83 per cent during this period. Carbohydrate gruels employed varied, but consisted principally of those made from arrowroot, parched flour, and sago.

By the second semester, breast feeding had stopped in 41 per cent of East Indian, and in 33 per cent of Negro mothers, with a corresponding rise in the use of bottle feeding of cow's milk and of carbohydrate gruels. Various boiled root vegetables, including Irish potato and yam, were occasionally given in a mashed form. Bush teas were almost universal. Of other protein foods, small amounts of legume (dhal) were sometimes given by East Indian mothers. Eggs and meat were largely limited by cost; fish was more available in coastal regions.

Fig. 2*B*. Same child as in Fig. 2*A*. Edema of lower legs, hepatomegaly, thick subcutaneous fat. No rash or definite hair change.

Table I. Analysis by age group and mortality of 121 children in the first 2 years of life admitted to San Fernando General Hospital with a primary diagnosis of diarrhea (January to May, 1958). (Percentages given to nearest whole number)

Age (months)	*Diarrhea cases*		*Mortality (%)*
	No.	*%*	
Under 1 to 6	83	69	19
7 to 12	16	19	19
13 to 24	22	18	9

DISCUSSION

Over-all picture. It is plain that, while protein-calorie malnutrition in early childhood, including kwashiorkor, is a significant problem in San Fernando Hospital (serving, as it does all South Trinidad), it is in fact not very common in the community at large. This is supported by the fact that plotting of homes of children with kwashiorkor admitted to the hospital from 1956 through 1958 shows a wide scatter, which could be shown by superimposition of transparent acetate maps to correlate with population distribution. In addition, only 2 cases of kwashiorkor were seen in the field in the infants and preschool children combined, while the edema index was less than 1 per cent for infants and nil for preschool children, in contrast to a 7 per cent preschool edema index found in 1958 in a country-wide field survey of another West Indian island, Haiti.[5]

All other indices employed confirmed the comparatively low prevalence of protein-calorie malnutrition in the community by tropical standards. There was also little clinical evidence of the 2 classical textbook nutritional syndromes of temperate zone pediatrics, that is rickets and infantile scurvy. However, angular stomatitis, possibly related to riboflavin lack, was present in 5 per cent of all preschool age children, but was much

Table II. Annual admissions to San Fernando General Hospital with gastroenteritis and malnutrition (1956 to 1958)

Annual admissions	*1956*		*1957*		*1958*	
	No.	*% total*	*No.*	*% total*	*No.*	*% total*
Total nonsurgical (under 1 to 10 years)	1,544	-	2,171	-	2,275	-
Gastroenteritis (under 1 to 2 years)	191	13.4	318	15.7	493	22.8
Gastroenteritis (2 to 10 years)	16		27		26	
Malnutrition*	86	5.5	59	2.7	44	1.9

*Almost all below 3 years of age.

commoner in East Indians (8 per cent) than in those of African ancestry (3 per cent). Follicular hyperkeratosis (5 per cent) and Bitôt's spots (1 per cent) were also seen not infrequently in this East Indian group.

Age incidence and etiology. Analysis of results confirms that protein-calorie malnutrition and severe diarrhea are both conditions occurring most commonly in Trinidad in the first year of life. The lower age incidence of kwashiorkor, compared with figures from other Caribbean studies, is shown in Table V, in which the only lower average age of presentation at hospital was in the series reported from Panama City by Howard and Meriwether.[13]

Certain factors appear to be responsible, probably resulting from the recent ecologic changes in Trinidad as the island has developed from an exclusively agricultural peasant country to a partly industrialized, more sophisticated state. One important facet of the present findings is that it is likely that other tropical countries in the process of technical development may follow similar trends, possibly with worse results, as apparent adverse developments in Trinidad have been paralleled, and to some extent counterbalanced, by the beneficial effects of (1) a rise in prosperity as measured by earning capacity, (2) improved medical facilities and (although still insufficient) increasing child welfare clinics, (3) the availability of numerous brands of dried milk in all parts of the island, both in village shops and in limited quantities in child health centers.

That these 3 factors are among the more important that have caused the much lower incidence of classical-age kwashiorkor than, for example, in Haiti, where the opposite is the case. At the same time, certain factors have emerged which, at least in a small number of children, have resulted in a different pattern of malnutrition, with the emphasis on infantile kwashiorkor and the nutritional marasmus-infective diarrhea complex.

Failure of breast feeding. In the temperate zone, the last few decades have been characterized by a spectacular fall in incidence of breast feeding. More recently, this trend, following in the wake of technologic sophistication and urbanization, has commenced to invade the tropics, especially the towns, as shown by reports from West Bengal, India,[15] Lagos, Nigeria,[16] and Kampala, Uganda.[17] This unfortunate trend, which initially always involves the more sophisticated, westernized, well-to-do segment of the population, in Trinidad has also come to affect at least some of the relatively lower socioeconomic group village dwellers, as has also been reported from Panama.[13] The contrast between the usual tropical peasant woman's ability to breast feed uneventfully, is emphasized by a 95 per cent success rate at 6 months in rural West Bengal in a study conducted in 1955,[15] and the lower figure of 59 per cent in the 4 to 6 month children of

village mothers of East Indian descent in Trinidad, whose parents, it must be emphasized, had come originally from Bihar and Orissa, neighboring states to West Bengal in India.

Reasons for this failure are complex and are mainly related to interference with the delicate psychosomatic "let-down" reflex as a result of a variety of emotional factors engendered by: (i) a realization that there are nowadays many efficient and highly advertised milk preparations on the market, which are produced exclusively for infants, (ii) worry over the possibility of lactation failure, (iii) a lack of personal observation of babies being breast fed during the mother's own girlhood together with the fact, that, by modern convention, breast feeding is carried out in private and is, therefore, a social inconvenience, (iv) lack of a completely single-minded attitude toward breast feeding, as a result of alternative duties, pursuits, and amusements being available to emancipated women who wish to take a more active part in modern society, (v) the mother's anxiety not to lose her figure, especially the bust (which in the Western culture is the most stressed secondary sex characteristic), (vi) the influence of the rising importance of money in the value systems of an industrializing society, and therefore of "the things that money can buy, in preference to the things that Nature provides."[15]

In Trinidad, increasing sophistication and example of the predominantly bottle-fed infants of wealthier people play a part, aided by press and radio advertisements extolling a wide variety of infant foods of varying suitability, while a few doctors still appear to regard breast feeding as a harmless eccentricity and advise artificial feeding very readily. It is insufficiently realized that when a poor tropical mother stops breast feeding, her infant runs a sizable risk to health and even life.[8]

One of the most important factors in Trinidad is that mothers are nowadays going out to work more often, which has the double effect of interfering with breast feeding and

A *B*

Fig. 3. Atypical infantile kwashiorkor. East Indian girl, aged 6 months, showing (*A*) edema of hands, scattered flaky-paint rash, angular cheilosis, subcutaneous fat, and wasted muscles, with relatively normal hair, (*B*) edema of feet and lower legs, flaky-paint rash, and wasted muscles with overlying subcutaneous fat.

Table III. Protein-calorie malnutrition (P.C.M.) and certain miscellaneous findings in (1) infants Negro ancestry included.) (Percentages given to nearest whole number)

	Syndromes								*Gómez weight*								
									United States standards								
	Kwashiorkor		*Incomplete kwashiokor*		*Nutritional marasmus*		*Nutritional dwarfing*		*Norm*		*1st*		*2nd*		*3rd*		
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	
Infants																	
(under 1 to 12 mo.)																	
East Indian	2		2		2		0	0	74	47	69	44	11	7	3	2	102
Negro	0	0	0	0	0	0	0	0	70	82	15	18	5	6	0	0	71
Total	2	1	2	1	2	1	0	0	144	60	84	34	16	7	3	1	173
Preschool children																	
(1 to 4 years)																	
East Indian	0	0	0	0	2	<1	12	2	150	30	291	57	66	13	2	<1	96
Negro	0	0	2	1	0	0	9	3	195	62	105	33	19	6	1	0	81
Total	0	0	2	0	2	0	22	3	345	42	396	48	85	10	3	0	177

*Local standards only available for both groups up to 2 years of age.

also leaving the preparation and administration of the infant's food to an older sibling in the house or "boarding" him out with a rural grandmother.

While breast feeding is desirable for children anywhere, for poorer groups in the tropics it is necessary for the infant's survival, both as a source of protein and calories, and also as an uncontaminated food. This is stressed in the present series by the fact that all of 14 children with infantile kwashiorkor for whom dietary histories were available had had "nutritionally unsatisfactory" breast feeding, as noted previously, while 93 per cent of 64 babies in the first 6 months of life for whom histories were available had, because of failure of breast feeding, what may be termed, in tropical peasant circumstances, "bacteriologically dangerous" infant feeding.

Faulty infant feeding. Dietary histories of children admitted with protein-calorie malnutrition and with diarrhea showed that, as well as the failure of lactation, infant feeding was faulty, being made up of small quantities of very dilute milk and starchy carbohydrate gruels and paps. This general pattern was also commonly found during the actual community study (Table IV).

As a substitute for breast milk, infants often receive small amounts of dried milk, often of a popular, expensive brand with a low protein content, or of condensed milk. Precise information is difficult to obtain, but it was commonly claimed that a 1 pound tin of dried milk lasted as long as a month, a rate of consumption that would not provide an adequate intake for an infant weighing 3 pounds. In most cases, the milk was eked out by mixture with arrowroot or sago, but sometimes as the infant's condition deteriorated, glucose was added, apparently because of mystic virtues, probably associated with its high price. The common technique was summarized by the mother who said: "I feeds the baby arrowroot, but whitens it with milk."[1]

In particular, arrowroot (flour from the tubers of *Maranta arundinacea*) appeared to be especially popular as an infant food and, as it is almost pure starch with only negligible vegetable protein, it can be considered particularly "kwashiorkorogenic," recalling the *Mehlnährshaden* ("flour-feeding injury") of similar cases seen by Czerny and Keller in Central Europe at the beginning of the century.[18]

A faulty diet is usually given to a tropical infant for one or more of the following reasons[19]: (a) poverty, (b) incorrect ideas about certain foods, including prejudices and food attitudes which can act as "cultural

and (2) preschool children in the community. (Only children of predominantly East Indian or

classification								P.C.M. nutritional indices								Miscellaneous					
Local standards*																					
Norm		1st		2nd		3rd		Edema		Low arm circumf.		Hypochromotrichia		Pluckability		Follicular keratitis		Bitôt's spots		Angular stomatitis	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
102	65	46	29	6	4	3	2	2	1	–	–	0	0	0	0	0	0	0	0	0	0
71	84	10	12	4	5	0	0	0	0	–	–	0	0	2	1	0	0	0	0	0	0
173	71	56	23	10	4	3	1	2	1	–	–	0	0	2	1	0	0	0	0	0	0
96	57	60	34	7	4	1	1	0	0	–	–	4	1	0	0	25	5	5	1	38	8
81	79	19	19	2	2	0	0	0	0	46/304	15	9	3	9	3	8	3	0	0	9	3
177	65	79	29	9	3	1	0	0	0	–	–	13	2	9	1	33	4	5	<1	47	5

blocks," preventing the child from being offered even the limited range of foods available,[20, 21] (c) lack of knowledge of the nutritional needs of the growing child by the mother or, regrettably, sometimes by nurses and medical personnel.

In Trinidad, it is certain that primary poverty does not usually play the dominant role in the majority of cases, although a form of secondary poverty is often significant as a result of the broken homes due to shifting liaisons and illegitimacy. Indirect evidence for the former, apart from the general rather high standard of living in the island compared with other tropical regions (as shown by such material indices as clothes, shoes, bicycles, etc.) can be most strikingly emphasized by photographs and synopses of typical cases (Figs. 4*A* and 4*B*). In addition, it may be noted that dried skimmed milk is, in fact, available at child welfare clinics.

Food prejudices of significance as "cultural blocks"[20, 21] in relation to the development of protein-calorie malnutrition seem to be unimportant; in particular, no Hindu food attitudes appear to remain in third generation East Indians in Trinidad. Possibly the only obviously deleterious local food beliefs is that arrowroot (which is not even grown in Trinidad but is imported from the island of St. Vincent) is especially beneficial for infants, which may possibly date back to the concept in Victorian Britain that arrowroot was a particularly strengthening and "binding" food.

Diarrhea. Marked, probably infective, diarrhea (usually with "dry-season," fly-borne peak) seemed to be an antecedent factor in 48 per cent of cases of nutritional marasmus and of 18 per cent of cases of infantile kwashiorkor. Conversely, the majority of children under 2 years admitted with a primary diagnosis of diarrhea were malnourished, a considerable number being, in fact, classifiable as marasmic.

It is often impossible to disentangle the history of a child presenting in a marasmic state with coincident diarrhea. In many cases in Trinidad, it would seem to be a vicious circle produced by a diet deficient in protein and calories, given in the wrong dilution with contaminated feeding utensils→loss of weight→infective diarrhea→poorer food absorption, and sometimes therapeutic dietary restriction leading to marasmus, with probably increased susceptibility to infective diarrhea and so on.

Bacteriologic studies were not available in the present series, while the most striking feature of the histories available for 69 children under 6 months was that in 93 per cent their feeding was "bacteriologically danger-

A *B*

Fig. 4. *A,* Maternal component in infantile malnutrition. Infantile kwashiorkor in Negro boy aged 9 months. The mother stopped breast feeding at 2 weeks as she felt the milk was "too salt" for the baby who was fed on parched flour gruel and very little dilute dried milk formula. The family could have afforded more milk. Social diagnosis: lack of knowledge. *B,* Maternal component in infantile malnutrition. Infantile kwashiorkor in East Indian boy aged 5 months. Failure of breast feeding, diet mainly arrowroot. The mother was able to afford to buy milk. Social diagnosis: lack of knowledge.

ous," because of complete or partial failure of breast feeding, in either case necessitating bottle feeding.

A trend toward an increased incidence of severe infective diarrhea in early childhood in tropical regions in a transitional state of development has been emphasized by Verhoestraete and Puffer's analysis of mortality due to this disease in parts of South America[22] and by various publications noting the need for clinic rehydration centers, especially in urban areas, as in Caracas, Venezuela,[23] Santiago, Chile,[24] and Johannesburg, South Africa.[25]

This trend is also apparent in Trinidad; admissions to San Fernando Hospital for diarrhea in the first 2 years of life rose from 191 in 1956 to 493 in 1958. As elsewhere, the principal etiological factors responsible would appear to be a failure of complete breast feeding, faulty infant feeding and contaminated, unclean feeding utensils and food.[26]

The considerable nutritional and infective hazards of bottle feeding are not generally appreciated, whereas, in fact, artificial feeding in Trinidad usually means the provision of a dilute mixture of starch and water from a bottle that is sometimes washed, seldom scalded, and never boiled.

Statistics from a highly urbanized part of South Africa are particularly revealing, as they parallel present findings in Trinidad and very probably indicate what may well be the beginning of a trend in other rapidly changing tropical regions, where industrialization is being pressed as a means of raising the standard of living and, in consequence, a constant influx of population is occurring into what has been called the "septic fringe" of mushrooming towns. Thus, in Johannesburg,

the incidence of breast feeding has dropped among Bantu women, the age at onset of childhood malnutrition has become lower (32 per cent of kwashiorkor in the first year of life), and, in the pediatric unit of Baragwanath Hospital, patients admitted with malnutrition are only about half as many as those with severe diarrhea needing parenteral fluid therapy (72 per cent of whom are below 1 year of age, mostly with failure of breast feeding).[25]

Prevention. The prevention of protein-calorie malnutrition and of the increasingly important inter-related diarrhea of early childhood is certainly bound up principally with health education, which will mainly be imparted to mothers in Trinidad through public health visitors, in both the clinics and homes, so that expansion of these services is plainly of high priority. The content of the most suitable health education for the present-day Trinidadian scene would embrace the following 5 points: (a) the encouragement of breast feeding for the first 6 months to 1 year of life, (b) the use of dried milk preparations including inexpensive skimmed milk (which should continue in good supply because of the geographic nearness to the milk-producing United States) either reconstituted or mixed with foods, after the first semester of life (or, if breast feeding has failed, its correct use earlier), (c) dissuasion from using arrowroot as a nutritionally dangerous substance, (d) the introduction of a mixed diet based on local foods in the second half of the first year, and (e) the prevention of infective diarrhea by encouraging the use of clean feeding utensils and boiled water.

This health education directed toward mothers must be paralleled by an increased awareness of the twin problems of malnutrition and infective diarrhea by doctors and

Table IV. Aspects of infant feeding as judged by questioning 223 mothers in rural South Trinidad, with special reference to breast feeding. (Percentages given to nearest whole number)

Age groups (months)	*Total number*	*Breast feeding*						*Cow's milk*		*Carbohydrate gruel*	
		Fully		*Occasionally*		*Stopped*					
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
East Indian											
Under 1 to 3	39	35	90	0	0	4	10	21	54	4	10
Under 1 to 6	29	17	59	6	25	6	24	24	83	12	41
7 to 12	70	27	39	14	20	29	41	66	94	39	56
Negro											
Under 1 to 3	27	27	100	0	0	0	0	18	67	2	7
4 to 6	25	18	72	1	4	6	24	20	80	4	18
7 to 12	33	18	55	4	12	11	33	26	79	14	40

Table V. Range and average ages of children with kwashiorkor in various Caribbean islands (and in Panama City)

Author	*Date*	*Location*	*Age range (months)*	*Average age (months)*
Waterlow[11]	1948	West Indies (Trinidad, British Guiana, Jamaica)	4 to 16	10.5
Van der Sar[12]	1951	Curaçao	5 to 21	12
Howard and Meriwether[13]	1952	Panama City	1 to 17.5	6.9
Jelliffe, Bras, and Stuart[14]	1954	Jamaica	6 to 31	13
Present study	1959	Trinidad	2 to 32	8

para-medical personnel in the country. Health education often has to begin "at home."

SUMMARY

An investigation of malnutrition in early childhood was undertaken in South Trinidad in March, 1959.

Analysis of admissions to San Fernando General Hospital showed that 70 children had been admitted in 1958 with a primary diagnosis of malnutrition. None were over 3 years of age, only 10 per cent fell in the "classical" 1 to 3 year period, and the majority (86 per cent) were between 1 and 12 months of age. All were classified as having "protein-calorie malnutrition." Eighteen were suffering from kwashiorkor and of these 15 (83 per cent) were infants. Their dietary history, when available, showed that all had had what was in Trinidad "nutritionally unsatisfactory" breast feeding together with small amounts of various milk preparations and carbohydrate gruels, especially arrowroot. The peculiar clinical picture of infantile kwashiorkor is described.

Analysis of admissions with diarrhea also showed that the majority occurred below 2 years of age—69 per cent in the first semester of life. Dietary histories showed what can be termed in Trinidad as "bacteriologically dangerous" infant feeding in 93 per cent of infants.

The prevalence of protein-calorie malnutrition in the community at large was estimated by examining the total child population aged between birth and 4 years in 15 villages and 2 slum areas in the County of Victoria. Assessment was attempted by syndromes and by the use of certain nutritional indicators. Results showed relatively little protein-calorie malnutrition in the community at the time of the survey, the preschool edema index being nil.

Factors are considered which may be responsible for the change in age incidence of protein-calorie malnutrition from the classical 1 to 3 year period to infancy and of the increasing occurrence of diarrhea in early childhood. Unsatisfactory infant feeding associated with a decline in breast feeding and a lack of knowledge of correct methods by mothers appear to be of major importance.

Thanks are due to the Hon. Winston Mahabir, Minister of Health, Trinidad, and to Dr. Young Lao, Director of Medical Services, for giving permission to carry out the survey and for their kind support and assistance; and to Dr. Stella Abidh, M.O.H. Victoria, Dr. Landreth Smith, M.O.H., San Fernando, and to Dr. G. G. Smith, Superintendent Medical Officer, San Fernando Hospital. For actual detailed arrangements in the field we are most indebted to Dr. Elizabeth Quamina, Assistant M.O.H., Victoria, and to Nurse C. Forde of the Public Health Visiting Service, who assisted with all the field work.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 6-month-old female infant was admitted because of swelling of the abdomen which had progressed in the previous 3 days. Eight days prior to admission, the child was noted to be febrile, irritable, and vomiting; she was treated with Terramycin (10 mg., three times daily). Just prior to transfer here a paracentesis yielded clear fluid.

The previous history was unremarkable except for jaundice appearing at 24 hours of age, with the highest recorded bilirubin 13 mg. per cent, and with spontaneous subsidence over a 3 week period. This illness was thought to be caused by ABO blood incompatibility (maternal blood type, O Rh positive; paternal blood type, AB). There was no evidence of omphalitis or other sepsis at that time.

On arrival at The Children's Hospital her temperature was 101.4° F., pulse rate 132 per minute, and respiratory rate 30 per minute. There was obvious ascites in the markedly distended abdomen. There was no jaundice. Moderate respiratory distress was presumed secondary to the marked ascites. No organs were palpated within the abdomen. No abnormality was found in the remainder of the physical examination.

Numerous studies were performed and included a paracentesis, at which time only enough fluid was removed for diagnostic study and relief of respiratory distress. This fluid was straw colored and clear with a specific gravity of 1.015, a total protein of 3.5 Gm. per cent (albumin, 2.4 Gm. per cent; globulin, 1.1 Gm. per cent). A Gram stain of sediment contained no bacteria and cultures for aerobic, anaerobic, and acid fast bacilli were subsequently negative. There were many erythrocytes and 500 nucleated cells per cubic millimeter, mostly mononuclear forms. There were no tumor cells on smear or block sections of a spun concentrate of this fluid. A stool was guaiac negative and contained trypsin in normal amounts. A sweat electrolyte test was normal. Hematologic studies showed a hemoglobin of 9.3 Gm. per cent; leukocyte count of 20,000 per cubic millimeter with 41 per cent polymorphonuclear leukocytes, 14 per cent band forms, 36 per cent lymphocytes, 3 per cent eosinophils, and 6 per cent monocytes. Urinalysis was not notable. Spinal fluid was normal. Numerous determinations of composition of blood were obtained: serum albumin, 3.7 Gm. per cent; serum globulin, 1.6 Gm. per cent; nonprotein nitrogen, 25 mg. per cent; indirect bilirubin, 0.2 mg. per

cent; total bilirubin, 0.4 mg. per cent, electrolytes normal except sodium ranging between 130 and 134 mEq./L.; serum amylase, 34.1 units (normal up to 150); serum lipase, 1.7 units (normal up to 1.5); cholinesterase, 30 mg. per cent (normal, 30 to 60 mg. per cent); prothrombin time, 49 per cent of normal.

Roentgenologic studies included a normal barium swallow and gastrointestinal series, a normal intravenous pyelogram, and essentially normal pulmonary fields. Evidence of marked ascites was noted in all of these films, with a trace of fluid in the left thorax. Enlargement of liver or spleen could not be detected radiologically.

A low sodium diet (less than 100 mg. daily) was offered but was refused and the child did poorly even on tube feedings.

Three weeks after admission, laparotomy was performed. Eight hundred milliliters of straw-colored fluid was removed. The liver was pale but otherwise unremarkable; a biopsy was taken. There was evidence of marked inflammation throughout the upper abdomen, particularly around the base of the transverse mesocolon where the bowel was matted together. There were several small pale opaque deposits in the peritoneum; one of them was biopsied. Pressures within the portal vein and portogram revealed no abnormality.

Postoperatively, she seemed to improve somewhat while receiving broad spectrum antibiotics but ascites reaccumulated. She was discharged 2 weeks after the operation.

At home there was little change in her condition for 2 weeks, but then she began to deteriorate, with poor dietary intake, lethargy, and increasing abdominal distention. She was readmitted 3 weeks after discharge in severe respiratory distress. She was now emaciated, with extreme abdominal distention, prominent venous pattern over the thorax, and pulsating neck veins. The blood pressure was 110/90 mm. Hg with definite pulsus paradoxus, tachycardia (pulse rate, 180 per minute), and rapid, labored respiration. A great amount of fluid was obviously present in the abdomen. The remainder of her physical examination was essentially unchanged from her previous admission.

Urinalysis showed no unusual findings. The blood contained 9.5 Gm. per cent hemoglobin; 37,500 leukocytes with 79 per cent polymorphonuclear cells, 18 per cent lymphocytes, and 3 per cent monocytes; 20 mg. per cent nonprotein nitrogen; 7.0 Gm. per cent total protein; 140 mEq./L. sodium, 5.2 mEq./L. potassium, and 104 mEq./L. chloride. No bacterial organisms were found in the 200 ml. of murky-brown fluid obtained on initial paracentesis. Although several attempts to remove additional fluid were made to relieve respiratory distress, only a few milliliters could be obtained at any one time.

X-rays of the chest and abdomen outlined considerable elevation of the diaphragm apparently secondary to intra-abdominal fluid. The heart was not enlarged, but only a small beat was noted along the left heart border on fluoroscopy.

One week after admission an operation was performed. The pericardium appeared normal when inspected through a small transthoracic incision. This was quickly closed and laparotomy was done.

DR. KENNETH WARREN.* We are presented with a puzzling illness in a 6-month-old girl who rapidly develops abdominal swelling. She had been well apart from an episode of jaundice as a newborn, and since jaundice is not subsequently part of her problem, I cannot fit this episode into the pattern of her more recent illness.

Now, 8 days prior to admission at 6 months of age, the infant had a febrile illness. The accompanying irritability might suggest the presence of abdominal pain. It would be interesting to know if the vomiting were particularly pernicious, such as might occur with an anomaly around the upper alimentary tract. One would anticipate a great deal of vomiting and a febrile course with acute pancreatitis. In the next few days abdominal enlargement was noted and clear fluid was

*Dr. Warren is Surgeon, Lahey Clinic, New England Baptist Hospital and New England Deaconess Hospital.

obtained by abdominal paracentesis. On arrival in this hospital she had vital signs in keeping with her degree of fever, showed no jaundice, and had marked ascites, probably capable of masking any visceromegaly which might have been present. I assume that the portion of the physical examination which is not described in detail includes a rectal examination which might have given quite important information concerning such things as dilatation of the colon, palpable mass, and so forth. We cannot know from the information given whether or not the child had ileus, which is a very prominent feature of inflammatory diseases of the gastrointestinal tract. Abdominal fluid was removed to ease respiration and for diagnostic studies. The fluid seems to be quite nondescript with specific gravity and protein content compatible with cirrhosis or renal disease. It might be compatible with a certain degree of inflammation of the pancreas in which there was no marked loss of pancreatic enzymes into the fluid. Probably the mononuclear cells described have been desquamated from the peritoneum, and suggest neither inflammation nor tumor. That tumor cells were not recognized does not help a great deal because, in terms of malignancy of pancreas or even of liver, these cell studies are frequently negative. Cultures were negative. May I ask if amylase determinations were done on this fluid?

DR. VAWTER. This was not done.

DR. WARREN. It would be important to know the value of this enzymatic activity. Stools were negative to guaiac testing and contained normal trypsin. For all practical purposes the laboratory data presented eliminate cystic fibrosis of the pancreas. Although the leukocyte count is elevated to 20,000 there is no great increase in the neutrophilic series. The normal urinalysis is important since if a patient has acute pancreatitis of the degree to cause this much ascites, there might also be a diabetic state or glycosuria, but not necessarily so. Serum protein, electrolyte, and bilirubin values were essentially normal. Serum amylase was only 34 units but this patient was being studied at least 8 days after the onset of illness so that, even if she had acute pancreatitis, the amylase could be normal and still the patient could go on to a fatal outcome. With acute pancreatitis the serum lipase, which is slightly elevated in this case, will remain elevated for a greater length of time than will the serum amylase, but at this level I cannot place much significance on this value. The cholinesterase level was low normal and the prothrombin time was somewhat depressed.

May I see the x-rays?

DR. E. B. D. NEUHAUSER. The chest film indicates nothing unusual. On an intravenous pyelogram (Fig. 1) the poorly outlined kidneys and the collecting systems appear normal, as does the bladder. The loops of bowel are not too abnormal in size or caliber but seem to be close together. On lateral films of the abdomen (Fig. 2) one gets an idea of how extraordinarily protuberant the abdomen is with a markedly elevated diaphragm.

Fig. 1. Normal intravenous pyelogram with centrally clustered loops of bowel surrounded by a "ground-glass" density.

The small amount of gas seen lies within the bowel and is evenly scattered. Later barium studies (Fig. 3) did not demonstrate esophageal varices but the stomach and duodenum tend to lie a little anteriorly perhaps. The size of the duodenal loop is within the upper limits of normal, but not definitely enlarged.

DR. WARREN. Except for ascites, there is nothing very remarkable in the x-rays. There may be some question of flattening out along the prepyloric area of the greater curvature of the stomach which one might anticipate to be related to an enlargement of the pancreas. In general, you will find, under those circumstances in which the mucosal pattern is ironed out, that a cyst is present or that the pancreas is markedly enlarged, with a very smooth and quite characteristic appearance. When the patient did not respond to medical management, laparotomy was done, with removal of almost a liter of straw-colored fluid. There was nothing to suggest cirrhosis in the liver, which was somewhat pale, perhaps in relation to anemia or to some degree of fatty infiltration. The evidence of inflammation through the upper abdomen and particularly around the base of the transverse mesocolon is very bothersome. Such involvement around the base of the transverse mesocolon is quite common in pancreatic disease, be it malignant or benign. We search carefully here for evidence of tumor spread when trying to determine whether a lesion is surgically resectable or not. In acute pancreatitis the first place to look for fat necrosis is at the base of the transverse mesocolon inferiorly, where the plaquelike lesions of possible fat necrosis were found in today's patient. However, in acute pancreatitis it is unusual to find extensive matting together of the small intestines. The process, which appears to have been principally inflammatory, may have been so extensive that perhaps the lesser peritoneal cavity was not opened. A great deal of information might be obtained from such an exploration but one must balance the hazard against the possible benefit.

One is a little surprised that the pressure within the portal vein was determined since

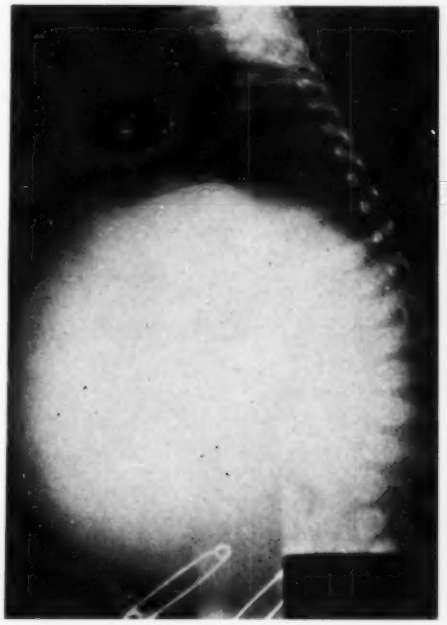

Fig. 2. Lateral abdominal film to show density of massive fluid accumulation.

there is no description of venous engorgement or splenomegaly. It makes a great deal of difference whether the pressure was measured directly in the portal vein, where it may be normal, as against readings of the splenic or mesenteric vein, where the pressure may be tremendously elevated in some types of pancreatic disease or in thrombosis of either of these veins. The same considerations apply to the injection of radiopaque material: if it was injected centrally into the portal vein some obstructive lesion might be missed in one or another tributary vessel.

DR. W. HARDY HENDREN. These studies were made through the portal vein.

DR. WARREN. In any event, this little girl did not really improve. Instead she began once more to have serious abdominal distention and so was readmitted. I wonder about the chest x-rays on this second admission in view of the pulsus paradoxus, the venous distention, and comments concerning the cardiac beat.

Fig. 3. In the x-ray film of barium swallow and follow-through, there is possible anterior displacement of the stomach and widening of the duodenal loop.

DR. NEUHAUSER. I did not show the film because there did not seem to be any important change in size or contour of the cardiac silhouette (Fig. 4).

DR. WARREN. This is difficult to reconcile with those findings, which certainly seem to justify the steps which were finally taken to exclude pericarditis. The laboratory data are not strikingly different than before, and may in part be explained by a degree of dehydration. The abdominal fluid had changed to a brownish fluid, which might indicate the presence of blood rather than fecal material from a perforated viscus since no bacteria were found in the fluid.

One of the most striking aspects of this case is the persisting marked abdominal distention despite many unsuccessful attempts to remove the fluid. Perhaps the adhesions previously noted are in some way responsible for loculation of this fluid.

I had hoped that the chest x-ray taken at this time might have disclosed the apparen enlargement of the cardiac shadow which i sometimes seen in patients who have acut pancreatitis and who subsequently develo either cysts or abscesses which migrate int the posterior mediastinum. Such a migrating structure, were it present, might well shift the heart or compromise the systemic venous return in such a way as to produce the evidences of interferences in systemic venous return which might lead to pulsus paradoxus and subcutaneous venous distention.

Taking all these points together, I think one must try to rule out cirrhosis for which we have little or no positive evidence in this case. Furthermore, the data given would tend to rule out obstruction of the portal vein. I assume then that the pathology rests in the region of the pancreas. Both sarcoma and carcinoma of the pancreas are rare in childhood. I could find only 10 cases of carcinoma in the pancreas under the age of 20. One of those I saw in a patient 11 years old and Dr. Walter Becker has removed one in a child 18 months of age. We have no positive evidence for any of the parasitic diseases which might account for this clinical picture. I believe, therefore, that this child had a type of pancreatitis, perhaps even with complicating pseudocyst formation, either process perhaps playing a role by virtue of inflammation or pressure effects in producing partial obstruction of the splenic vein or the superior mesenteric vein, or both, with development of ascites.

DR. ALEXANDER NADAS. I was just as puzzled about the possibility of this degree of ascites as a result of cardiac disease in a patient with a heart as small as this. In the textbook you will see that very severe right heart failure may occur in a patient whose heart is clinically not greatly enlarged; in fact as many as 75 per cent of cases may show this.

DR. NEUHAUSER. We thought the heart was small and suggested that the patient had severe hypovolemia.

DR. NADAS. Ordinary pericarditis seems excluded and, furthermore, constrictive peri-

carditis must be very rare at this age, if indeed it ever has occurred. Probably the venous pressure is not so high as the described venous distention suggests and certainly the portal pressure was normal, so that the main puzzle left is the existence of pulsus paradoxus. I think that in a good many patients following operation, one may see a slight to moderate degree of pulsus paradoxus, and in these there is usually no question of pericarditis. I don't think I have ever seen this much ascites on a cardiac basis without evidence of edema somewhere else.

Dr. Warren. Will ascites per se account for this finding?

Dr. Charles A. Janeway. I have an impression, subject to a lot of question, that we see a degree of pulsus paradoxus under a variety of circumstances, as for instance, in occasional patients with nephrosis who have the diaphragm pushed up high. We see it even in asthmatic patients. This seems to mean that many processes which interfere with systemic venous return to the chest are capable of producing this pattern which, after all, reflects the amount of blood delivered to the heart.

Dr. Harry Shwachman. One wonders what this child's nutritional status is—since she showed a rather low nonprotein nitrogen in the presence of a high protein level presumably secondary to dehydration.

Dr. R. J. Haggerty. We did not come as close as Dr. Warren has, in several weeks of watching this patient. First, we thought of some inflammatory disease but discarded this in favor of portal vein obstruction when all the bacteriologic studies were in. This is why there were so many examinations of the upper gastrointestinal tract and this was the approach we had in determining to do an exploratory laparotomy.

Dr. Hendren. We were, as the protocol has indicated, quite perplexed. At the first surgical exploration, the findings of lesions resembling fat necrosis and inflammation at the root of the transverse mesocolon seemed entirely consistent with pancreatitis. However, the great accumulation of ascitic fluid was thought unusual for simple pancreatitis. Therefore, we went ahead with the pressure evaluation and radiopaque studies of the portal vein as described. We also searched carefully for a possible anomaly of the small bowel, such as a duplication of the jejunum, because about 2 years ago we encountered such a patient who had developed pancreatitis when a jejunal diverticulum ruptured into the lesser sac, causing pancreatitis, portal vein thrombosis, and later, portal hypertension. We found no such abnormality and rather than chance stirring up more trouble, decided to close the abdomen after taking biopsies of the liver and a peritoneal plaque, but not the pancreas, for fear of causing a pancreatic fistula.

When she returned for the second time, we too thought that our failure to remove much fluid might be attributable to loculations formed by adhesions. Because there were some clinical features suggestive of constrictive pericarditis and because of having previously encountered a child with poly-

Fig. 4. Massive abdominal fluid on second admission with normal or small cardiac silhouette.

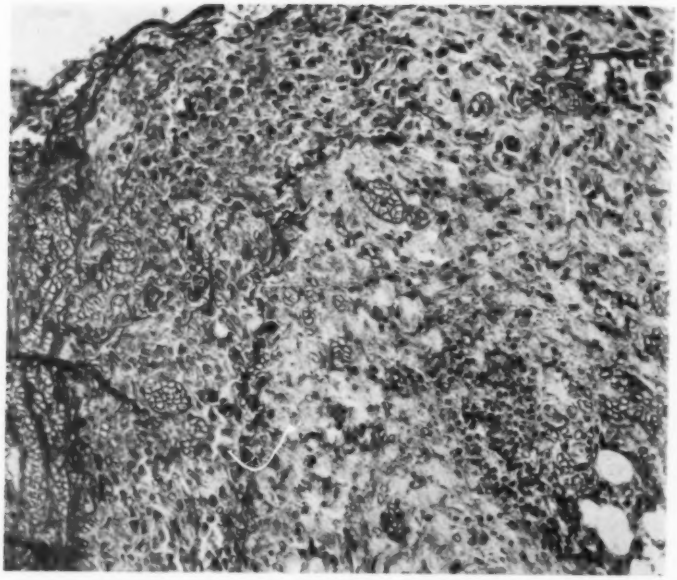

Fig. 5. Vascularization, fibrin deposition, hemorrhage, and mononuclear response in peritoneal plaque at first operation. (Toluidine blue–eosin stain. ×250; reduced ½.)

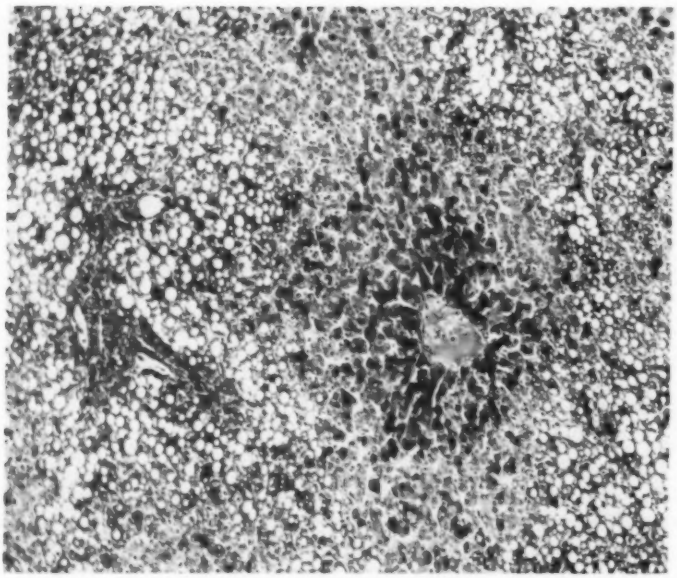

Fig. 6. Periportal fatty infiltration in liver biopsy at first operation. (PAS stain. ×115; reduced ½.)

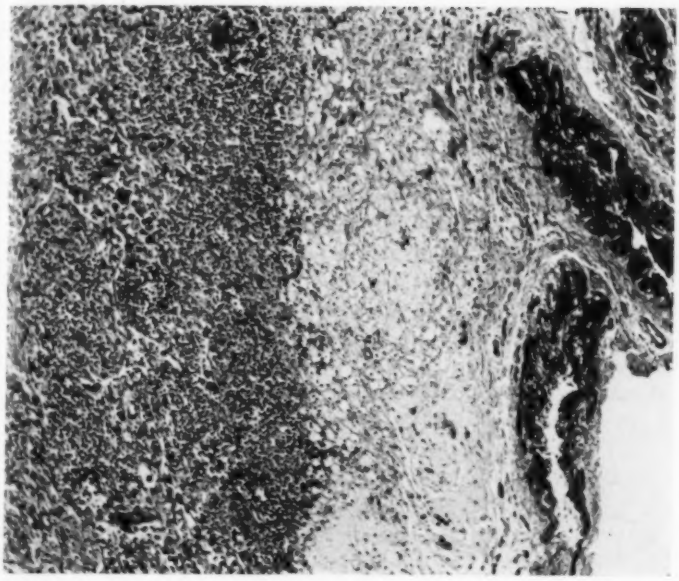

Fig. 7. Margin of lymph node removed at second operation. The zone of pallor consists of marginal sinus filled with foamy macrophages undergoing necrosis. (PAS stain. ×115; reduced ⅓.)

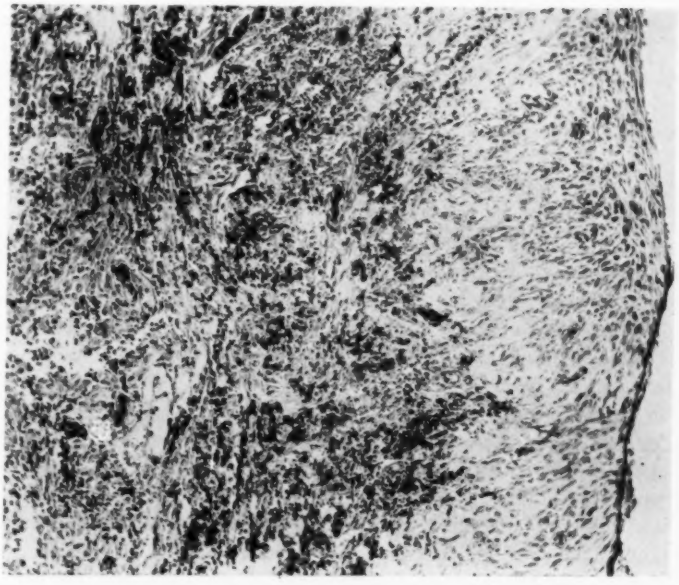

Fig. 8. Wall of pseudocyst. No epithelium is present. The appearance is that of a relatively bland reparative process beneath a superficial zone of fibrin (on right). (Toluidine blue–eosin stain. ×115; reduced ⅓.)

serositis who had both constrictive pericarditis and ascites, we decided first to take a quick look at the heart to rule out positively the correctible entity of constrictive pericarditis. When that was found to be normal, laparotomy seemed mandatory. This time, to our surprise, after opening the abdomen, we found no free fluid at all, but instead a very large pancreatic pseudocyst[1] which had formed following the pancreatitis. This cyst was located behind the stomach in the lesser peritoneal cavity and was so large as to account for the massive abdominal enlargement and very well could have compromised the abdominal venous circulation, as already discussed. This cyst was treated by internal drainage of the cyst by means of a Roux-en-y jejunal loop.

Now, several months later, the child is having no further abdominal difficulties. She has fairly normal stools, although we have kept her on Viokase since there was at first some evidence of deficiency of pancreatic enzyme secretions, manifest by bulky, foul stools.

DR. VAWTER. With all of the data in, we feel that this case best fits as an example of *pancreatitis with complicating pseudocyst* at an extraordinarily young age.

At the first operation a biopsy of a peritoneal plaque near the pancreatic bed shows a chronic and active peritonitis with outpouring of fibrin and a mononuclear response (Fig. 5). The tissue beneath has the "smeared" dead appearance one sees with proteolytic digestion. However, there is no fat or calcification in this biopsy. There is no evidence of scar, vascular abnormality, or inflammation in the biopsy of liver. There is periportal fatty change (Fig. 6) which may have more than one pathogenesis. If trypsin is removed from the stool, protein is no longer adequately digested, and there may develop one or more amino acid deficiencies as for instance, methionine deficiency. The proteolytic activity found in this patient's stool does not completely exclude this mechanism. Moreover, the periportal distribution of fat might suggest a direct toxic injury of various possible origins such as might occur with certain intra-abdominal infections or with circulation of the products of tissue necrosis and digestion. This differs, in any case, from the fatty liver of the adult patient who has pancreatitis where complicating alcoholism and diabetes mellitus are frequent problems.

In a lymph node from the second operation, there is evidence of lymphatic stasis with masses of foamy cells probably representing phagocytosis of breakdown products of adipose tissue. These cell masses (Fig. 7) are undergoing necrosis by a process histologically suggesting proteolytic activity which may arise from a damaged pancreas or by lymphatic drainage from the pseudocyst. Finally, there is no epithelial lining in the wall of this pseudocyst which is formed by nondescript granulation tissue, layered over by zones of fibrin (Fig. 8). All of these patterns fit, I believe, into those we might expect in pancreatitis and complicating pseudocyst.

I would like to throw open the question of etiological factors.[2] Many of the cases we see at autopsy have no clear explanation and repeatedly bacteriologic and current virologic exploration, principally by Dr. Sidney Kibrick, has given no clues since, even though we find instances of pancreatitis in infants with Coxsackie virus infection, this is uncommon. Trauma is an important factor in pancreatitis in children. The obstructive lesions of the pancreatic ducts are intriguing since there are many reports of pancreatic ducts plugged with roundworms. Dr. L. K. Diamond assures me that hemorrhagic pancreatitis rarely, if ever, overshadows the principal illness in patients with general hemorrhagic diseases. There is some evidence that dietary indiscretions will precipitate attacks of pancreatitis. Perhaps this is not so far removed from those rare metabolic states associated with abdominal crises. In deference to Dr. Shwachman, I will not suggest that acute pancreatitis is important in pancreatic fibrosis, certainly not after advanced atrophy of the exocrine tissue is apparent.

DR. HENDREN. We have also seen pancreatitis secondary to a common duct stone in a child with congenital hemolytic anemia.

There is an occasional case following blunt abdominal trauma in childhood.

DR. WARREN. I do not subscribe to any single theory of the etiology of pancreatitis since the evidence points to there being innumerable causes, but I believe, too, that intrapancreatic obstruction and infection play the larger roles. In this child, perhaps the most attractive mechanism might begin with an infection leading to duodenitis, and thence to involvement of the pancreatic duct, which may have become occluded and partly necrosed by the inflammation, and so on.

DR. JANEWAY. Have any patients with mumps pancreatitis required surgical intervention?

DR. HENDREN. Not that I know of. This is usually a mild disease lasting 3 or 4 days and subsiding with no late complications, such as occurred here.

DR. VAWTER. In the literature about 1 to 2 per cent of patients with mumps and pancreatitis have serious illness and occasionally victims of this group die.

DR. R. CANNON ELEY. Very often one will see a child with mumps who, before any parotid swelling occurs, will complain of abdominal pain with some vomiting or cramps, and the spilling of a little sugar in the urine will be observed. Just as one starts to treat the acute diabetes, the parotitis appears and clarifies the diagnosis.

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COMMENTS ON CURRENT LITERATURE

Perinatal mortality associated with evidence of toxoplasmosis

NATURAL toxoplasmic infection is found all over the world in a wide variety of species, including those of mammals, birds, and reptiles. Carriers of this intracellular protozoan parasite, *Toxoplasma gondii,* occur among domestic animals and birds, including dogs, cats, sheep, goats, swine, cattle, rabbits, rats, guinea pigs, domestic fowl, and pigeons. The association of chronically infected dogs excreting toxoplasma and human infection has been reported. Experimental infection of sheep and lambs with a strain of toxoplasm obtained originally from naturally infected sheep has been described recently in *Lancet.*[1] Infection was possible by intravenous, intraperitoneal, and inhalation routes, and the organism was found to persist in the brain, skeletal and heart muscle, liver, and kidney. With respect to meat consumption, however, the ordinary cooking process is considered sufficient to kill the organism.

Infection in the human subject may be congenital or acquired; both forms are characterized by a wide variety of clinical patterns ranging from an almost completely asymptomatic course to a generalized infection with fatal outcome. The chief clinical manifestations of congenital toxoplasmosis include fever, chorioretinitis, abnormal spinal fluid findings, convulsions, intracranial calcification, anemia, jaundice, splenomegaly, and hepatomegaly. Acquired toxoplasmic infection in older children and adults may be asymptomatic or mild, or may be characterized by fever, pneumonia, myocarditis, and encephalitis with evidence of meningeal involvement, or by fever and lymphoadenopathy with a maculopapular type of rash, in which case the condition may resemble infectious mononucleosis. Infection with toxoplasma organisms is followed by the formation of neutralizing and complement-fixing antibodies, and by the development of a delayed type of skin sensitivity elicited by the intradermal injection of antigen. The dye test employing methylene blue which was devised by Sabin and Feldman provides a quantitative as well as a very sensitive method for the detection of neutralizing antibodies against toxoplasma.

With respect to pathogenesis, the changes observed in the human subject vary with age. In the fetus and the young infant the principal pathologic change consists in a marked destruction of nervous tissue; other tissues invaded by the parasite include the heart, lungs, adrenal glands, and striated muscles. In severe infection of the fetus or newborn infant the meningoencephalomyelitis may be characterized by large inflammatory lesions with necrosis, and by calcification and cyst formation. The areas involved include the cortex, subcortical white matter, the caudate and lenticular nuclei, midbrain, pons and medulla, and the spinal cord. Severe lesions are likely to occur around the ventricles. The chorioretinitis may be marked by edema and necrosis of the retina. In a few instances toxoplasma organisms have been cultured from the tissues of stillborn infants, or fatal

infection of the fetus has been suspected on the basis of characteristic necropsy findings.

A recent issue of the *British Medical Journal* carries a report of considerable interest in this respect. This report by Robertson[2] deals with excessive perinatal mortality, observed in a small town, which was found to be associated with evidence of toxoplasmosis. "During the years 1956, 1957, and 1958, large and persistent differences were noted between the perinatal mortality rates for three adjacent districts in North Lincolnshire."[2] These differences were found to stem from variation in stillbirth rates in the respective districts. Over a three-year period, 1956 to 1958, the small town of Barton-on-Humber suffered a stillbirth rate of 59.6 (proportion as per 1,000 births). In the same triennium "the neighboring town of Brigg enjoyed the exceptionally favorable stillbirth rate of 9.0, while the surrounding rural district experienced a rate of 28.1."[2] Statistical analysis showed these differences in the number of stillbirths to be significant. Accordingly, investigations were carried out in "an endeavour to ascertain the cause of the excess stillbirths experienced in Barton-on-Humber."[2] These investigations, which included any environmental factors, chemical, physical, or biological, in which the towns might vary, were partly retrospective and partly prospective. Control and "stillbirth" groups of mothers were compared first as to age and parity. Although concordance in these respects was not perfect, it was found to be remarkably good.

While both these communities are small market towns within 11 miles (17.7 km.) of each other, certain topographic and biologic differences were immediately apparent. Barton-on-Humber is situated on a tide-river bank where salt marshes and brackish water provide a breeding ground for mosquitoes, whereas Brigg is located 10 miles inland on the banks of the River Ancholme, a much less favorable breeding ground for mosquitoes. There is some difference in the nature of the industries of the two towns, the principal industries of Brigg being fruit canning, sugar refining, and hosiery manufacture, and those of Barton, the manufacture of bicycles, chemicals, ropes, and bricks. Where mothers continued to work during pregnancy, the nature of the work was investigated. Very few mothers in either the control or the "stillbirth" groups undertook to work during the pregnancy. Genetic factors are difficult to investigate and evaluate; however, no obvious genetic defects were uncovered in either group in this study.

Possible infectious disease factors were investigated thoroughly. Syphilis was not found to be a factor in the incidence of stillbirths in this area. Rubella, influenza, respiratory illnesses, and other virus diseases had been at an unusual minimum during this particular triennium. It seemed to the investigators that "the most probable biological agent would be an infection whose rate of spread was slow, and which was either symptomless or which produced vague or minor illness of a type seldom recognized."[2] On a number of occasions during the years in question routine milk testing had shown that cattle in the area were excreting *Brucella abortus*. In 1957 investigations by Beattie[3] had indicated that toxoplasmosis was prevalent in Lincolnshire. Accordingly studies were initiated with respect to both these diseases. Beattie offered to perform toxoplasma dye tests on blood specimens from mothers of stillborn infants, "control" mothers of liveborn infants of the same period, and on expectant mothers. About this time the toxoplasma studies received impetus from the fact that one "stillbirth" mother (early 1956) gave birth to an infant with mild clinical manifestations possibly caused by toxoplasma infection.

The present report deals primarily with the retrospective aspects of the toxoplasma study. Women who were resident in Barton-on-Humber, and who had stillborn infants during 1956, 1957, and 1958 were identified and traced. The "control" mother for each "stillbirth" mother was one who had never had a stillborn infant, and whose present liveborn infant had been delivered in the same month as the corresponding stillborn

infant. Detailed study was possible on 19 such pairs of mothers. The questionary was designed to obtain information with respect to past obstetric history, consanguinity between parents, occupation of the father, details of work outside the home, illnesses during pregnancy, dental treatment, anesthetics, x-ray, and medical treatment for whatever reason, drugs administered, recreational habits, and contact with animals, in addition to details of the pregnancy under review. Detailed information was available for all 38 mothers, and its compilation was the joint effort of the patient and her family, the doctor or midwife in attendance, and the district nurse, plus information obtained from hospital records. None of the mothers of stillborn infants in the group investigated gave a history of previous stillbirths. Three of the mothers had experienced previous abortion, and among the control group there were 2 mothers with such a history. One mother who was delivered of a stillborn infant had lost a former child at the age of 7 months as a result of hydrocephaly. Two of the mothers in the "stillbirth" group were sisters; their sister-in-law (brother's wife) had also produced a stillborn child early in 1955. However, no evidence of a genetic factor could be obtained in this family. Seven of the mothers in the "stillbirth" group experienced some degree of toxemia of pregnancy as compared with 4 of the "control" mothers. Two of these toxemic mothers gave birth to hydrocephalic stillborn infants.

Serologic findings for both groups of mothers are presented in tabular form. Unfortunately brucella agglutination procedures were not carried out on all of the control specimens. However, since only 2 of the "stillbirth" group showed positive tests for brucellosis, the author concludes that this disease can be eliminated safely as a major factor in causing the excess of stillbirths during the period in question. Dye-test titers for toxoplasmosis varied between the two groups; most of the blood specimens from mothers of the stillborn children were positive above $\frac{1}{32}$, whereas most of the control specimens were negative at $\frac{1}{16}$. These differences proved to be statistically significant. In some instances, however, the titers were lower than is to be expected if infection with toxoplasma has been recent, an observation which can be accounted for in part by the fact that the study described here is of the retrospective type. As the author points out, "It is impossible, in a retrospective investigation of this kind, to prove that toxoplasmosis was responsible for any particular stillbirth in the series. A statistical association such as this could result if toxoplasmosis and the true cause of the stillbirths were both related to a third factor, such as a common means of transmission. Nevertheless, the most probable explanation of the facts observed in this investigation is that toxoplasmosis was responsible for a proportion of the stillbirths."[2]

In the past toxoplasmosis has not been regarded as a significant cause of stillbirths; in the present instance, however, the author feels that this infection is the most probable cause, since the two groups of mothers were remarkably similar in other respects, parity, age, etc. "A more extensive investigation of all pregnancies occurring in the three districts of Lincolnshire during 1960 is at present in progress. . . . In addition, an attempt is being made to examine all the 300 children who were born in Barton-on-Humber during 1956-58, in order to detect and treat any congenital infection. Confirmatory evidence that toxoplasmosis has been unusually prevalent in Barton-on-Humber may be obtained as a result of this work."

RUSSELL J. BLATTNER, M.D.

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Books

Diseases of the Newborn.

Alexander J. Schaffer, M.D., Philadelphia, 1960, W. B. Saunders Company, 878 pages. Price $20.00.

Dr. Schaffer, a pediatrician with a wealth of experience in the care of newborn infants, has fulfilled the purpose of this text very well. It is written primarily from the clinical viewpoint and is directed to the practitioner of pediatrics who for a long time has needed a reference book devoted to the newborn infant. The author admits that detailed information about pediatric physiology, pathology, and embryology is lacking and refers the reader to appropriate sources for additional information.

The subject matter is completely covered; the chapter on the examination of the newborn infant is excellent; in some instances pathology is treated superficially. The material is presented in a lucid manner with the author frequently quoting personal experiences and presenting case histories illustrating important clinical conditions with editorial comments. These features impart a lecture-type style to the text which is effective as a teaching exercise. The book contains numerous roentgenograms and those illustrating pathologic conditions of the pulmonary and gastrointestinal systems are excellent and are of value in the differential diagnosis of many of the clinical problems. The photomicrographs are good. Special chapters devoted to the differential diagnosis of neonatal dyspnea, anemia of the newborn, icterus, and enlarged kidney, conditions which frequently overtax the pediatrician, are excellent and are useful as a handy reference. The bibliographies following each chapter are good and of recent origin. The appendixes on the nursery management, the care of an erythroblastotic infant, resuscitation, and the pharmacopeia are useful.

One may take issue with several statements in the text: "Prematurity is still the primary cause of death in more than half of the newborns who succumb for all reasons." Several pediatric pathologists have shown that when careful postmortem examinations are performed, bacteriologic specimens obtained, and the clinical course reviewed, a cause of death other than prematurity can usually be assigned. In the appendix on resuscitation, the author recommends the rockette. To this reviewer, this apparatus has never proved to be of value.

This text is recommended to the physician working with newborn infants and to medical students as a reference book.

NORMAN KENDALL, M.D.

The Development of the Infant and Young Child, Normal and Abnormal.

R. S. Illingsworth, M.D., Edinburgh and London, 1960, E. & S. Livingstone, Ltd. (in U. S., Williams & Wilkins Company, Baltimore), 318 pages. Price $6.50.

This well-prepared 300 page book is an excellent contribution to current pediatric literature. It provides a useful review of the former studies, both foreign and American, in the fields of mental retardation, pediatric neurology, and growth and development.

Dr. Illingworth has formulated a good reference text for those who work with the mentally retarded and physically handicapped child.

His approach is a clinical one stressing important factors in history, physical examination, and associated congenital defects that permit definitive diagnosis or aid in management. The book reflects the author's clinical experience. Many of the unusual reflexes of newborn infants are discussed. There are pictures and tables of growth and development which are of particular value in the differential diagnosis of the cerebral palsied or retarded child. There is also a good discussion of the "brain-injured" child. Many of the newly recognized inborn errors of metabolism, endocrine problems, and enzymatic defects are mentioned. Aberrations in the sequence of development, both normal and abnormal, are presented, including those associated with sensory defects or psychiatric discrepancies.

The author freely quotes and admittedly borrows from Arnold Gesell and the workers of the

Yale Clinic of Child Development, but adds a clinical concept to their studies, giving them much needed practical application. His stressing the value of Gesell's observations is encouraging to those who feel that his work has contributed to a better understanding of the patterns of growth and development.

This book is not meant to be an all-encompassing text of pediatric neurology. It's greatest use should be for pediatricians and allied workers in the fields of the handicapped, cerebral palsied, and neurologically involved infants and young children.

MILTON SARSHIK, M.D.

Medical Care of the Adolescent.

J. Roswell Gallagher, M.D., New York, 1960, Appleton-Century-Crofts, Inc., 369 pages. Price $10.00.

This book is a landmark, as it fills a definite gap in the voluminous literature on adolescence and the adolescent. It is written for physicians rather than for workers concerned with the many other aspects of adolescence. While many have contributed to our knowledge of some one phase of the medical care of the adolescent, or one disease, the subject is so broad and the medical problems involve so many special fields, it would have been almost impossible for any one author to cover the subject as a whole had it not been for the unique pioneer, Adolescent Clinic of the Children's Medical Center in Boston. Here, under the leadership of Dr. Gallagher, a group of physicians representing nearly a score of special medical fields have been working together for several years and educating one another. It is this background that has made it possible for Dr. Gallagher to author a general text for physicians on the medical care of the adolescent.

The first four chapters alone would have made a valuable short monograph for the physician as they cover the knowledege that a physician must have of the adolescent, the growth and development during the period, and the psychological reactions that color adolescence and make it unique. And they include an excellent practical discussion of the office visit, which is based on experience. This is necessary background material for the physician regardless of the particular medical condition. These are followed by chapters on the treatment of specific conditions and diseases which the admitting complaints at the clinic show occur with some degree of frequency. These cover a wide variety of nonrelated medical conditions such as epilepsy, acne, postural and orthopedic conditions, obesity, amenorrhea and dysmenorrhea, athletic injuries, enuresis, dyslexia, and so on. While here and there some statements may be open to discussion, these are quite unimportant. Throughout the book Dr. Gallagher stresses attitudes: the attitude of the adolescent to his disease or trouble, which differs from the attitude found in the age periods of childhood and maturity, and the attitude of the adolescent to the physician and vice versa. If therapy is to be of help and successful in the adolescent, it is essential that the approach and attitude of the physician permit the establishment of a satisfactory interrelationship between patient and doctor. It is this viewpoint, based on experience, that the author gives to the discussions of specific conditions, which makes the text unique and of great value to the practicing physician. The book is clear and well written and should be of great help to the pediatrician who follows his patients into the adolescent period and to the internist who takes over from the pediatrician. It is highly recommended.

BORDEN VEEDER, M.D.

Correspondence

To the Editor:

Although I humbly submit that I originally negotiated for the special issue of THE JOURNAL OF PEDIATRICS in honor of Lawson Wilkins, volume 57, September, 1960, I had not anticipated the pleasure of having an acknowledgment on the cover. Under the circumstances I feel obliged to express my indebtedness to other individuals. Various contributors to this volume cooperated in a scheme of mutual review of manuscripts. Especially, however, I must indicate the extraordinary assistance of Dr. Claude Migeon, Johns Hopkins Hospital. Dr. Migeon supplied me with a considerable body of information required for the organization of this issue and assumed full responsibility for all contributions from foreign authors. I feel that the issue would not have been possible without his generous and time-consuming help.

ALFRED M. BONGIOVANNI, M.D.
PHILADELPHIA, PA.

To the Editor:

Recently there has been increasing evidence, substantiated by striking and convincing statistics, that heavy smoking presents a real health hazard. We pediatricians, by the nature of our training, are probably more prevention minded than physicians in most other fields. Therefore, it occurs to me that the problem of smoking among our adolescents offers a new challenge in the field of prevention.

Dr. L. E. Burney, the Surgeon General, has summarized the existing information on the relationship of lung cancer and smoking (J. A. M. A. 171: 1829, 1959). He emphasized the fact that the nonsmoker has a much lower incidence of lung cancer in all controlled studies, whether analyzed in terms of rural areas, urban regions, industrial occupation, or sex.

The American Heart Association has recently stated (J. A. M. A. 173: 1130, 1960) that the death rate in middle-aged men from coronary heart disease was 50 per cent to 150 per cent higher among heavy cigarette smokers than among those who did not smoke.

The association between heavy smoking and diseases of the lung and heart cannot be disregarded, although precise etiological information is not yet available. I believe it is unnecessary to have such precise information before pediatricians take an unequivocal stand against smoking. We must educate our adolescents about the danger of smoking *before* they develop a habit which is detrimental to good health.

The health problem of adult smokers is not alarming enough for us to insist that people who cannot easily give up smoking be deprived of their pleasure. But the statistics are sufficiently serious that we should assume the responsibility of preventing our youth from starting on this unhealthy habit.

We pediatricians regularly discuss accident prevention and sex hygiene with our patients and their parents. Now we should and must include in our routine a serious discussion aimed to discourage smoking.

After all, we prevent tetanus by immunization though tetanus was never a significant health problem even before the routine use of prophylaxis. We have taken a most commendable course in the control of poisoning by disseminating information through our poison control centers. Let us be as prevention minded in the field of lung cancer and coronary disease, by alerting our adolescents to the dangers of smoking.

WALTER PICK, M.D.
FITCHBURG, MASS.

To the Editor:

Should a third year of training in straight pediatrics be required by the American Board of Pediatrics?

For the past 40 years (since September, 1920) I have been actively engaged in the private practice of pediatrics and in teaching medical students. One might say that pediatrics began to be considered a specialty about 1920. Infant feeding was the rock on which the specialty was founded. There was really very little to distinguish the pediatrician from the general practitioner in the beginning except for the pediatrician's superior

knowledge of infant feeding. There were probably less than 100 doctors in the country who limited their work to the care of children. The only hospital training that was considered necessary in 1920 was 1 or 2 years of rotating internship and 6 months to 1 year of pediatric training.

Since 1920 the growth of pediatrics has been phenomenal; probably more rapid than that of any other specialty. The bulk of knowledge which the young doctor has had to master has increased by leaps and bounds. By 1934 when the American Board of Pediatrics was founded, the required hospital training had risen to 3 years—2 years of pediatrics and 1 year of rotating internship or 3 years of straight pediatrics. These training requirements have remained the same to this day.

Medical knowledge has continued to grow at a rapid rate. Subspecialties have developed in the pediatric field, such as cardiology, allergy, hematology, dermatology, and psychiatry (behavior). In 1934 two years provided ample training for a man to learn what was then known about pediatrics. However, 2 years is not sufficient time for a young doctor to get the training in the subspecialties which he will now need when he goes into practice. For this reason I think a third year of pediatric hospital training should be required. During this last year he should get special training in the subspecialties mentioned above.

J. W. BRUCE, M.D.
UNIVERSITY OF LOUISVILLE
SCHOOL OF MEDICINE
LOUISVILLE, KY.

To the Editor:

I wanted to compliment Dr. Helmut R. G. Seckel on his presentation of a most interesting case in the August, 1960, issue of THE JOURNAL OF PEDIATRICS and am distressed to note that the commendation must be made posthumously.

His paper, "'Premature Thelarche' and 'Premature Metrarche' followed by Normal Adolescence," was based on careful, well-documented observations which are reported in a very interesting and lucid manner. The purpose of this communication, however, is to point out the fascinating correlation between his observations in his patient and our existing understanding of normal psychosexual development with its genital phase roughly between the ages of 4 and 7, and the latent period followed by normal adolescence and puberty. It would be most interesting to know the details of the patient's interpersonal relationships during these periods and how closely they actually correlate with the reported physiologic changes.

Is it conceivable that such end-organ responses could follow excessive or unusual psychic stimulation mediated through the hippocampal gyrus–lateral hypothalamic nucleus–endocrine pathway? No conclusions can be drawn at this point but the facts as they appear are certainly fascinating, and I am indebted to Dr. Seckel for his presentation.

R. DEAN CODDINGTON, M.D.
RED BANK, N. J.

To the Editor:

The matter of wider use of generic names for drugs is a popular subject in both legislative and medical circles.

There is another facet to the generic name story that has not received much attention. This relates to the situation that the editorial policy of some publications has the peculiar propensity for using only the generic name, without the accompanying trade name, when there is some direct, implied, or imaginary derogatory information concerning the drug discussed. However, they will use the trade name (alone) when the drug is introduced as a valuable new remedy or when the connotations are favorable. This is a disservice to the medical profession when the generic name is little known and there is a failure to recognize or associate the derogatory information with a product used by the casual medical reader. Both should be used, especially when only one firm makes the product. To juggle the nomenclature puzzle for reasons other than the prime one of making the facts involved clearly known is bad. No reasonable person would blame a drug involved in a suicide incident when ingested in massive overdose. On the other hand, this information should not be withheld by using obscure terminology, which unfortunately is the case when complex chemical names, or infrequently used generic names are used to the exclusion of the popular trade name. It is hoped that the present interest in the subject will result in better generic names.

HAROLD JACOBZINER, M.D.
THE CITY OF NEW YORK
DEPARTMENT OF HEALTH

News and notes

Traineeships are available in **Pediatric Research** to qualified individuals, who should have had at least 2 years of training or its equivalent in clinical pediatrics or medicine. The program is supported by the **National Institutes of Health** and is designed to prepare individuals for careers in full-time teaching and basic research in pediatrics. It is expected that a broad theoretical foundation for research will be provided as well as intimate experience with varied methodology. The complete program is a 3 year experience with initial emphasis on work under close supervision in a number of different laboratories and disciplines in the department as well as formal course work in other branches of the University. During the first 2 years, research will be carried out in the fields of biochemistry, physiology, virology, and genetics. Experience with tissue culture methods, enzymology, electrolyte physiology, chromatography, and tracer methodology will be provided. The third year will be devoted to research in one of these areas, and progressive, increasing independence will be encouraged. Fellows will not have clinical responsibilities. However, research dealing with clinical problems and materials will be carried out in a number of the laboratories, and fellows are invited to all of the lectures and conferences of the department.

Applications and requests for further information should be addressed to: Director of Training Program, Department of Pediatrics, The Johns Hopkins Hospital, Baltimore 5, Md.

Two **Fellowships in Pediatric Cardiology** will be available in the Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, beginning July 1, 1961. During the first year of the 2-year program, emphasis will be placed on training in currently available techniques for diagnosis and clinical investigation such as phonocardiography, electrocardiography, vectorcardiography, angiocardiography, cardiac catheterization, cineangiocardiography, dye dilution curves, radioisotope dilution curves, and respiratory physiology techniques. During the second year, the Fellow will explore further research methodology more intimately either by working as part of the research team devoted to pediatric cardiology or in a research project of his own choice. The program has been organized in close cooperation with the Departments of Radiology, Physiology, and Surgery.

Candidates should have completed 2 or more years of pediatric training. The stipend is $4,000.00 for the first year and $5,000.00 for the second year. Applicants should write to Jerome S. Harris, M.D., Chairman, Department of Pediatrics, Duke University School of Medicine, Durham, N. C.

A program dealing with all phases of medical care for adolescents will be held at **Tulane University School of Medicine** Feb. 8 to 11, 1961. The approach will be multidisciplinary with participation by the Departments of Pediatrics, Medicine, Psychiatry, and Surgery; emphasis will be placed on informal discussion and patient conferences to augment lecture material. Dr. Ross Gallagher, of Boston, will be the guest speaker.

The **Pediatric Service of The University of Texas,** M. D. Anderson Hospital and Tumor Institute, offers a clinical Fellowship in **Pediatric Oncology,** July 1, 1961, for one year (appointments may begin January 1 or July 1). The Fellowship carries 3 months' accreditation for the American Board of Pediatrics. The yearly stipend is $3,600. Send inquiries to Grant Taylor, M.D., The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston 25, Texas.

The **Raymond Blank Memorial Hospital Association** will sponsor a Pediatric Conference April 7 and 8, 1961, at the Younker Memorial Rehabilitation Center of the Iowa Methodist Hospital, Des Moines, Iowa. The fifth Lee

Forrest Hill Lectureship will be given by Ralph Platou, M.D. Other guest speakers will be C. Henry Kempe, M.D., James N. Etteldorf, M.D., and Jack Metcoff, M.D.

Registration fee for the entire course will be $20.00 and for a partial course, $10.00. Dinner and entertainment have been planned for wives. For additional information contact Charlotte Fisk, M.D., Chairman, 3200 University Avenue, Des Moines 11, Iowa.

La Cátedra de Pediatría y la Escuela de Postgraduados in Sevilla is offering the following courses under the direction of Dr. Manuel Suárez in 1961: Seminar on Practical Pediatrics for general practitioners, February 2 to 4; Infant Neuropathology, March 6 to 16; and Recent Advances in Pediatrics, May 2 to 6. For further information contact Cátedra de Pediatría, Secretaría de Cursos, Apartado 514, Sevilla, Spain.

Obedience Means Safety for Your Child, a booklet recently prepared by the **Accident Prevention Committee of the American Academy of Pediatrics,** should be a useful adjunct to the pediatrician in his efforts to educate parents in the prevention of accidents in childhood. The members of the Accident Prevention Committee of the Academy are to be complimented for their excellent efforts in this difficult area.

EDITOR'S COLUMN

"Physiologic" mental deficiency

DESPITE increasing study of many aspects of mental deficiency, research on the major unsolved problem in mental retardation has interested few physicians. Psychologists, educators, and social workers have contributed most of the recent literature concerning the familial defective. The thesis has been accepted without critical evaluation that such children represent the lower end of a normal frequency distribution of inherited intellectual capacity.

Unquestionably, intellectual capacity, like stature, has a multifactorial genetic basis. On the other hand, intellectual performance as measured by tests is not a biologic attribute and many factors other than genetic endowment may contribute significantly. Few data are available to assess the relative importance of various influences.

The diagnosis of familial or physiologic mental deficiency is based on a positive history of inadequate social adjustment in the parent or parents (usually the mother), absence of obvious physical stigmas, and relatively uniform depression of performance on psychological testing. Recent psychological studies by Gallagher,[1] however, indicate that there are many similarities in test response between children with brain injury and familial defectives. The epidemiologic studies of Pasamanick and Lilienfeld[2] have clearly demonstrated a relationship between mental retardation and complications of pregnancy. Likewise, a higher incidence of pregnancy complications (toxemia, pyelitis, prematurity) occur in a population of lower socioeconomic standing. Prenatal and perinatal injury may therefore account for some of the cases of "physiologic" mental retardation.

Statistical evidence for postnatal physical damage to offspring of defective parents is lacking. However, the frequency of cases of subdural hematoma, malnutrition, or hypernatremia in such patients in a clinic practice of pediatrics is striking.

Retardation on a basis of inadequacy of social and intellectual environment would seem to be of even greater importance. Unfortunately, existing longitudinal studies of offspring (especially defective twins) reared in different environments are inadequate. The evidence is clear-cut that deprivation seriously affects the individual with normal intellectual endowment. Nothing is known of the susceptibility to deprivation of the infant with marginal capacity to adjust. Relatively little study of the impact of environment on the intelligence level of offspring of defective parents has been carried out since the work of Skeels[3] almost a generation ago. Kirk's[4] recent study has validated to a certain extent the finding that the I.Q. may be depressed by poor environment.

If the evidence is incontrovertible that the I.Q. of the offspring of the defective individual can be elevated to that of the average (I.Q. 100) by early placement in a proper environment, programs for early detection and treatment must be established. Pediatrics, neurology, and public health agencies must be concerned with procedures, techniques, and instruments for far earlier detection than the present average of 8 to 10 years. Detection by history alone might be possible if physicians were sensitized to the merits of a detailed evaluation of the social adequacies of the parents of each patient. As soon as the probability of environmental damage is established, a new environment should be considered. Foster homes through which these children rotate like migrant workers cannot serve as a therapeutic facility. If stable foster homes cannot be obtained, the development of a new type of institution providing group living as in the U. S. S. R. must be undertaken, and the effectiveness of such institutions should be studied.

If the evidence is not clear-cut in regard to environmental improvement of the defective subject (and I believe that it is not), carefully controlled studies must be developed and supported by appropriate agencies. The possibility that the social and intellectual performance of a large segment of the population might be significantly improved justifies the cost of such research.

ROBERT E. COOKE, M.D.

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Microhemagglutination technique for the assessment of vaccines

Elsewhere in this issue Levine, Wyman, Broderick, and Ipsen describe a practical application of the hemagglutination technique for measuring the antibody response to diphtheria, tetanus, and pertussis antigens. Their technique has three advantages: (1) It requires only milliliter quantities of blood which can be obtained by simple lancet prick, a major advantage in pediatric practice where vaccines have their greatest usefulness; (2) the hemagglutination technique is reliable when compared to the accepted standard technique of rabbit intradermal testing; and (3) this type of testing is economical.

The publication of this work is timely since there is presently a need for careful evaluation of the efficacy of bacterial vaccines which are being combined in various ways with each other and with viral antigens. It is relevant to speculate whether this microtechnique might be applicable to mass field testing of viral vaccines.

MARTHA D. VOW, M.D.

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In chronic disorders associated with obstructed respiration, the dependable antispasmodic and expectorant action of Quadrinal rapidly clears the bronchial tree. Patients breathe more easily and acute episodes of bronchospasm are often eliminated. Quadrinal is well tolerated, even on prolonged administration. The potassium iodide in Quadrinal provides an expectorant of time-tested effectiveness and safety.

Indications: Bronchial asthma, chronic bronchitis, pulmonary fibrosis, pulmonary emphysema.

Quadrinal Tablets, containing ephedrine sulfate (24 mg.), phenobarbital (24 mg.), "Phyllicin"* (theophylline-calcium salicylate) (130 mg.), and potassium iodide (0.3 Gm.).

Also available—
a new Quadrinal dosage form with taste-appeal for all age groups:
fruit-flavored QUADRINAL SUSPENSION (1 teaspoonful = 1/2 Quadrinal Tablet)

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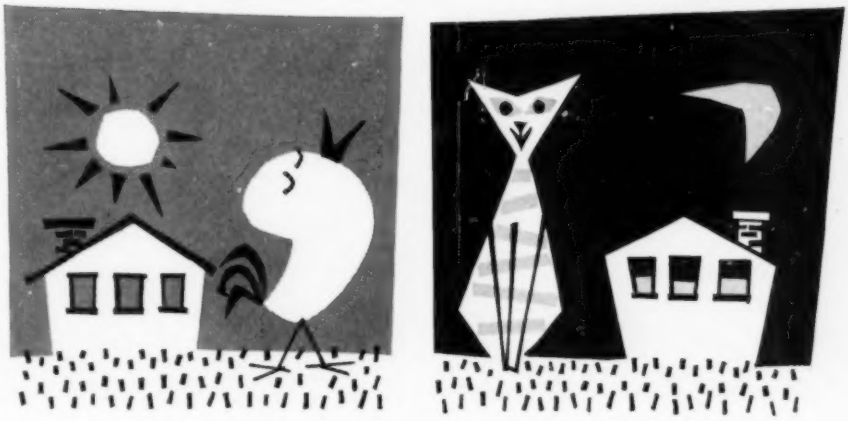
*Quadrinal, Phyllicin®

Just one (1) capsule tranquilizes

all day or all night



Here is *single-capsule convenience* for your tense, nervous patients.

One capsule at breakfast relieves both mental and muscular tension *all through the day.*

One capsule in the evening provides restful sleep *all through the night.*

Prescribe Meprospan for safe and convenient *sustained* tranquilization . . . less trouble for your patient, less chance to forget medication.

Meprospan®-400

400 mg. Miltown® continuous release capsules

Supplied: *Meprospan-400*, each blue-topped, *continuous release* capsule contains 400 mg. Miltown (meprobamate, Wallace).

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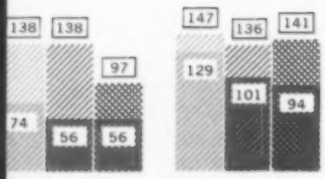
Phenethicillin (capsules)

Phenethicillin (tablets)

Lined areas represent fasting levels; shaded areas depict levels after food.

Number of times serum can be diluted and still inhibit
Staphylococcus 209P[1]
(average of 12 subjects)



"Blood Levels" vs. "ABA"

McCarthy and Finland's conclusions extend and confirm their previous observations[2] and those of Griffith.[3] They demonstrate that phenethicillin gives higher "blood levels" in micrograms, but, in terms of antibacterial activity in the serum ("ABA"), potassium penicillin V is clearly superior against the common pathogens (streptococcus and pneumococcus) and at least equal against the staphylococcus.

Furthermore, they show that these high antibacterial levels for potassium penicillin V are less severely affected by food. Thus, whether taken before meals or after, potassium penicillin V provides greater assurance of therapeutic activity.

What does high "ABA" mean to you?

High serum levels of antibacterial activity mean fewer treatment failures in severe infections or in infections only marginally sensitive to penicillin. In other words, high "ABA" means . . .

consistently dependable clinical results

V-CILLIN K®

(penicillin V potassium, Lilly)

intense antibacterial activity

V-Cillin K produces greater antibacterial activity in the serum against the common pathogens than any other oral penicillin.[1-3]

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No form of penicillin has been shown to be less allergenic or less toxic than V-Cillin K.[4,5]

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Documented experience with penicillin V and potassium penicillin V reveals the clinical excellence of V-Cillin K.[6-29]

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Otrivin relieves stuffy nose by decongesting the engorged mucosa, re-establishing *comfortable* nasal airways. Its action is not only gentle but prompt and prolonged, with little or no rebound congestion or other side effects. *Complete information sent on request.*

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DOSE: One tablet per day

SUPPLIED: Bottles of 50 tasty "Cherro-Chew" tablets.

REFERENCES:

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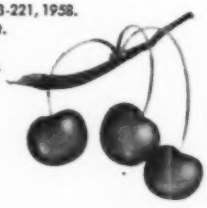

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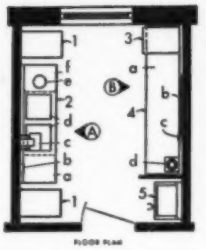

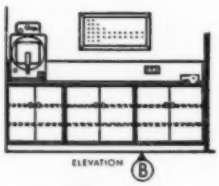

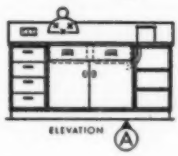

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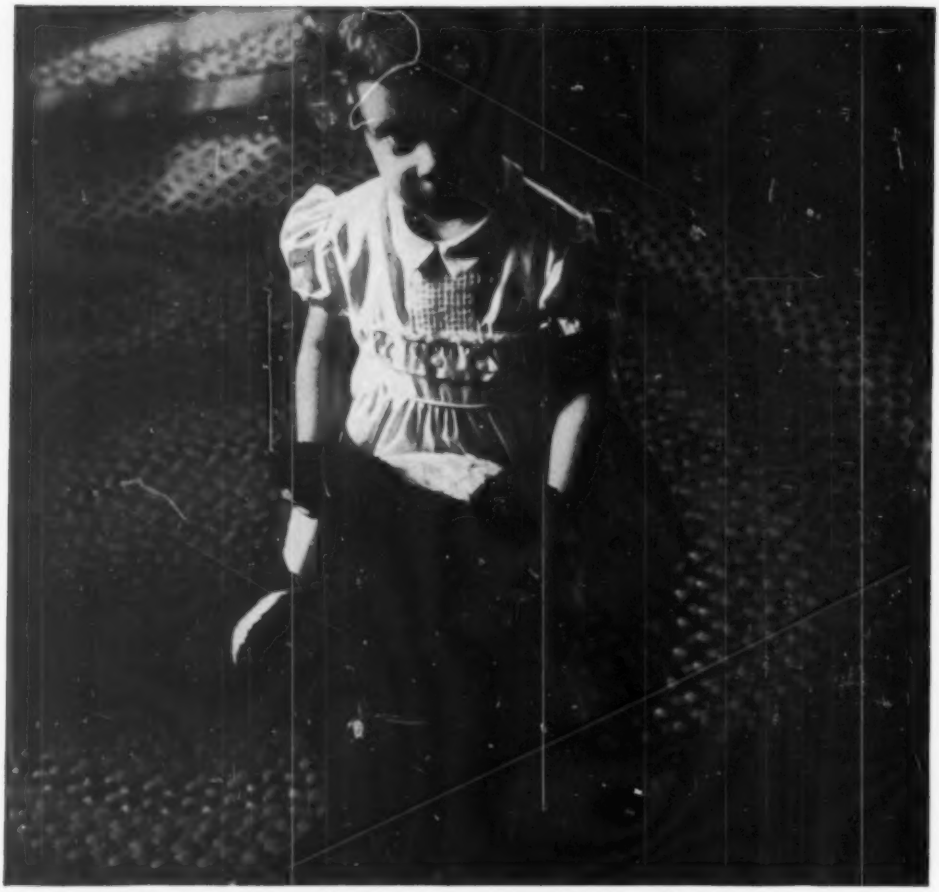

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1. Robertson, E. G.: *Postgrad. Med.* 25:31, Jan., 1959.

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References: 1.Epstein, N. N.: Eczema, Allergic, in Infants and Children (Atopic Dermatitis) : in Current Therapy, 1960. 2. Senear, F. E., and Haeberlin, J. B., Jr.: M. Clin. North America, March 1958. 3. Brunsting, L. A.: Postgrad. Med. 26:431, 1959.

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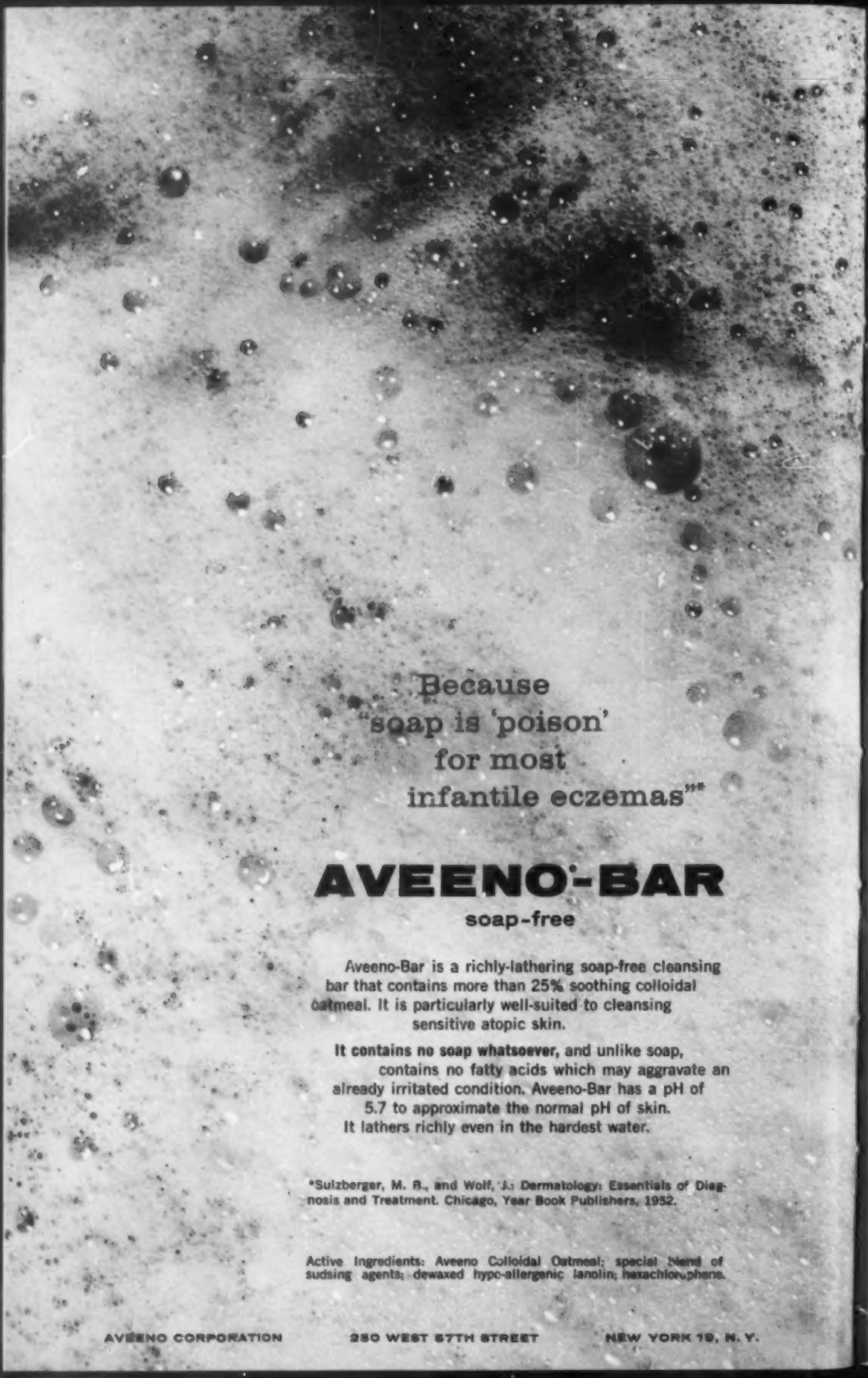
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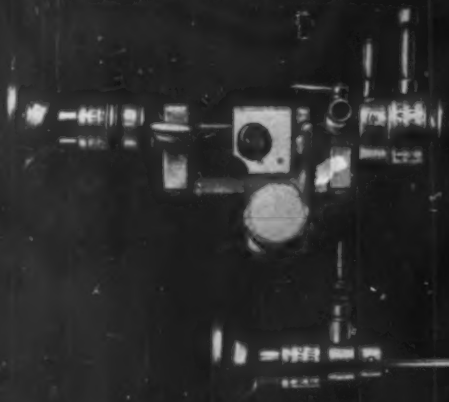

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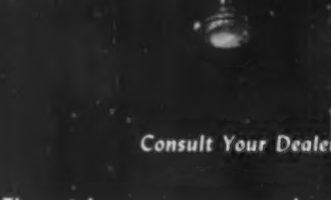

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- No barbiturate depression
- No suppression of adrenal function

Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydroalcoholic vehicle (alcohol 20%).

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3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

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Effective against more than 30 of the commonly encountered pathogens, including **staph** and **strep**, Panalba KM assures you of prompt control in potentially-serious pediatric infections. Panalba KM makes a pleasant-tasting, readily accepted suspension.

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AN ADDITION TO THE CALDESENE® FAMILY

FOR DIAPER RASH / MINOR SKIN IRRITATIONS

Caldesene Medicated Ointment and Powder are equally effective for the relief of itching, soreness, and burning of **Diaper Rash, Minor Skin Irritations** and **Prickly Heat.** Both contain 15 per cent calcium undecylenate for sustained antibacterial and antifungal action. The protective coating formed by Caldesene Ointment and Powder keeps moisture and irritants from coming in contact with the baby's tender skin.

Supplied: Caldesene Powder — 2 oz. shaker containers. Caldesene Ointment — 1½ oz. collapsible tubes in a water-washable base.

Maltbie

Maltbie Laboratories Division
Wallace & Tiernan Incorporated
Belleville 9, New Jersey, U.S.A.

PCD-03

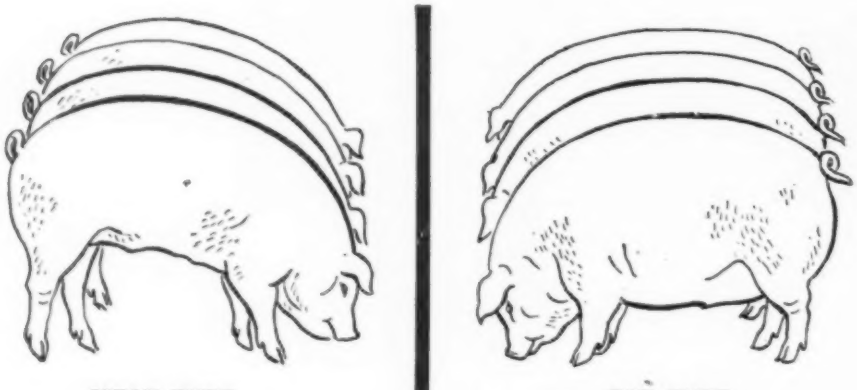
MEAT TYPE ANIMALS

A Scientific Development

Can you remember when "fat" was an ear mark of blue ribbon hogs, steers and lambs?

Today, after years of breeding and feeding techniques, through the teamwork of farmers, agricultural scientists and meat processors, firm meat-type animals have been developed.

Meat type animals, more lean meat and less fat, comply with medical diet requirements. Roasts, chops and steaks, offered at meat counters are leaner, closer trimmed, from meat type animals, bred and fed for a higher quality protein ratio.



MEAT TYPE

FAT TYPE

A Great Advance in Animal Agriculture!

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

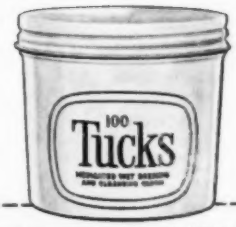
AMERICAN MEAT INSTITUTE

MAIN OFFICE, CHICAGO • MEMBERS THROUGHOUT THE NATION

WOOD is WONDERFUL
...for woodpeckers

but certainly not as a toilet wipe when anal areas are sensitive. Unlike harsh, dry wood pulp toilet papers, *Tucks* are soft cotton flannel pads mildly medicated with witch hazel (50%) and glycerin (10%). *Tucks* are ideal for routine toilet care when treating pruritus ani et vulvae, diaper rash, hemorrhoids, following episiotomy or hemorrhoidectomy, and in other anorectal conditions. *Tucks* cleansing, mildly astringent action hastens healing and helps assure patient comfort. *Tucks* are available at busy *prescription pharmacies* everywhere in jars of 40 and 100.

fuller **FULLER** *Pharmaceutical Company*



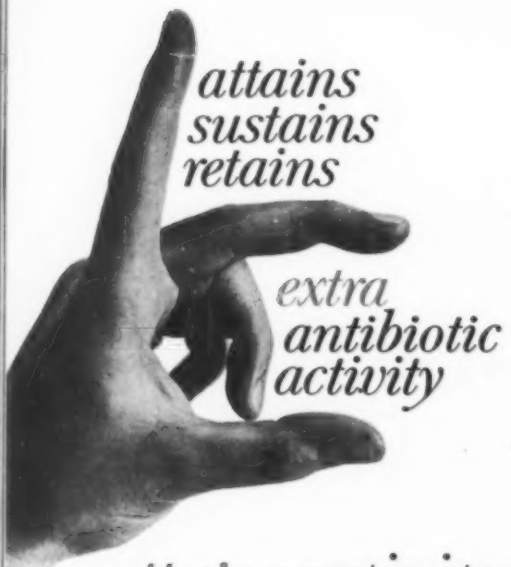
For a generous office supply of TUCKS—just fill in and return this coupon.

Name.....

Address.....

City.....Zone....State.....

Fuller Pharmaceutical Co.
3108 W. Lake St., Minneapolis 16, Minn. 55



attains
sustains
retains

extra
antibiotic
activity

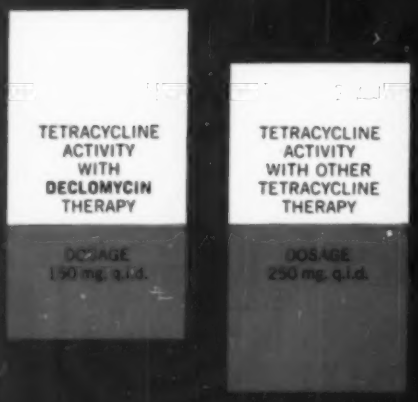
DECL

attains activity levels promptly

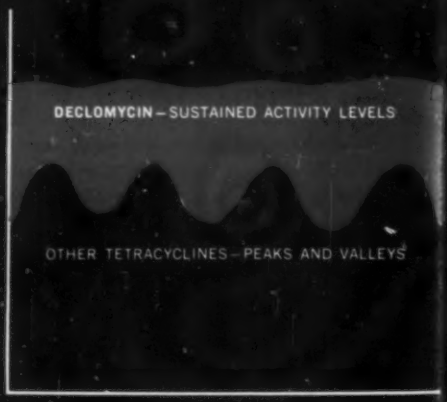
DECLOMYCIN **Demethylchlortetracycline attains—usually within two hours—blood levels more than adequate to suppress susceptible pathogens—on daily dosages substantially lower than those required to elicit antibiotic activity of comparable intensity with other tetracyclines. The average, effective, adult daily dose of other tetracyclines is 1 Gm. With DECLOMYCIN, it is only 600 mg.**

sustains activity levels evenly

DECLOMYCIN **Demethylchlortetracycline sustains, through the entire therapeutic course, the high activity levels needed to control the primary infection and to check secondary infection at the original—or at another—site. This combined action is usually sustained without the pronounced hour-to-hour, dose-to-dose, peak-and-valley fluctuations which characterize other tetracyclines.**


TETRACYCLINE ACTIVITY WITH DECLOMYCIN THERAPY
DOSAGE 150 mg. q.i.d.
TETRACYCLINE ACTIVITY WITH OTHER TETRACYCLINE THERAPY
DOSAGE 250 mg. q.i.d.

POSITIVE ANTIBACTERIAL ACTION



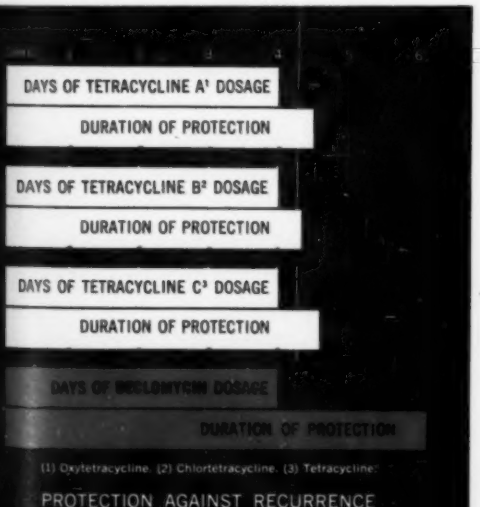
PROTECTION AGAINST PROBLEM PATHOGENS

CLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

retains activity levels 24-48 hrs.

DECLOMYCIN Demethylchlortetracycline retains activity levels up to 48 hours after the last dose is given. At least a full, extra day of positive action may thus be confidently expected. The average, daily adult dosage for the average infection—1 capsule q.i.d.—is the same as with other tetracyclines... but **total** dosage is lower and duration of action is longer.


DAYS OF TETRACYCLINE A¹ DOSAGE
DURATION OF PROTECTION
DAYS OF TETRACYCLINE B² DOSAGE
DURATION OF PROTECTION
DAYS OF TETRACYCLINE C³ DOSAGE
DURATION OF PROTECTION
DAYS OF DECLOMYCIN DOSAGE
DURATION OF PROTECTION
(1) Oxytetracycline. (2) Chlortetracycline. (3) Tetracycline
PROTECTION AGAINST RECURRENCE

CAPSULES, 150 mg., bottles of 16 and 100. **Dosage:** Average infections—1 capsule four times daily. Severe infections—Initial dose of 2 capsules, then 1 capsule every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. **Dosage:** 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into 4 doses.

SYRUP, 75 mg./5 cc. teaspoonful (cherry-flavored), bottles of 2 and 16 fl. oz. **Dosage:** 3 to 6 mg. per pound body weight per day—divided into 4 doses.

PRECAUTIONS—As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication.

Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under constant observation.

LEDERLE LABORATORIES
A Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York

a new antitussive molecule

NON-NARCOTIC

ULO®

Chlophedianol HCl

SYRUP

cough suppressant action	equal to	narcotics	Though it reaches peak action somewhat more slowly, the cough-suppressant power of ULO is fully as great as that of narcotics.
duration of action	greater than	narcotics	After reaching peak action, ULO maintains its maximal cough-suppressant effect undiminished for 4 to 8 hours.
side actions	less than	narcotics	ULO is free from the limitations and undesirable side effects of narcotics... no constipation, no nausea, no gastric irritation, no appetite suppression, no tolerance development, no respiratory depression, no drowsiness.

Indications: Upper respiratory infections • Common cold • Influenza • Pneumonia Bronchitis • Tracheitis • Laryngitis • Croup • Pertussis • Pleurisy

There are no known contraindications. Side effects occur only occasionally and are mild.

Dosage

Adults: One teaspoonful (25 mg.) 3 or 4 times daily as required.

Children: 6 to 12 years of age, ½ to one teaspoonful (12.5 to 25 mg.) 3 or 4 times daily as required.

2 to 6 years of age, ½ teaspoonful (12.5 mg.) 3 or 4 times daily as required.

Availability

ULO Syrup, 25 mg. per 5 cc. (teaspoonful), in bottles of 12 fluid ounces.

Riker Northridge, California

WHAT BABIES NEED...

ABDEC® DROPS

comprehensive multivitamin formula

for vitamin protection during the early years of rapid growth

Each 0.6 cc. supplies:	
Vitamin A	5,000 units
Vitamin D	1,000 units
Vitamin C (ascorbic acid)	50 mg.
Vitamin B_1 (thiamine hydrochloride)	1 mg.
Vitamin B_2 (riboflavin)	1.2 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.
Pantothenic acid (as the sodium salt)	5 mg.
Nicotinamide (niacinamide)	10 mg.

In 15- and 50-cc. bottles with calibrated plastic droppers. 32860

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

PARKE-DAVIS

Fostex® treats their acne while they wash

completely emulsifies and washes off excess oil from the skin.

penetrates and softens comedones, unblocks pores and facilitates removal of sebum plugs.

removes papule coverings and permits drainage of sebaceous glands.

Patients like Fostex because it is so easy to use. They simply wash acne skin 2 to 4 times a day with Fostex Cream or Fostex Cake, instead of using soap.

Fostex contains Sebulytic®,* a combination of surface-active wetting agents with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by sulfur 2%, salicylic acid 2%, and hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Fostex is available in two forms—

FOSTEX CREAM, in 4.5 oz. jars.

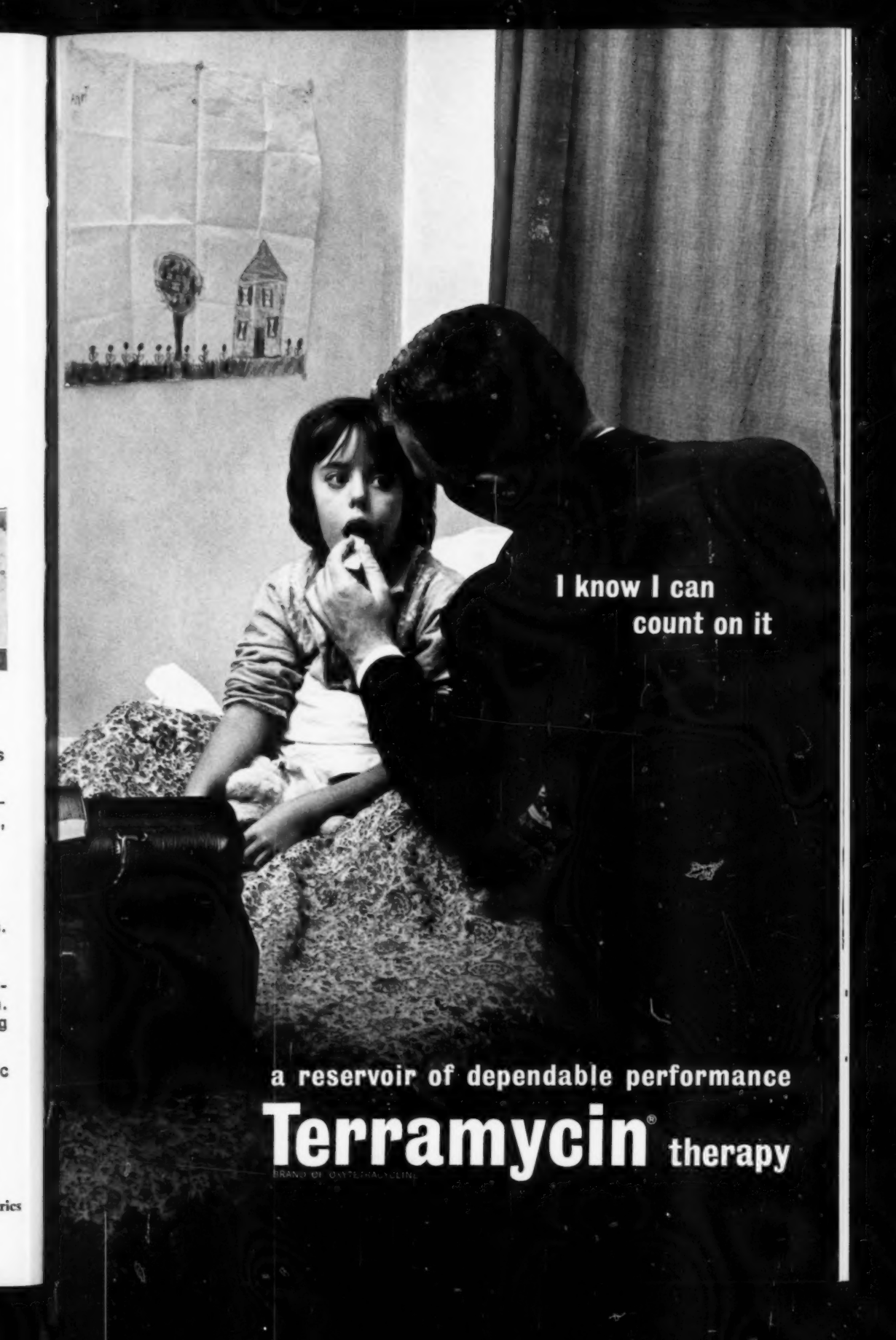
FOSTEX CAKE, in bar form.

Fostex Cream and Fostex Cake are interchangeable for therapeutic washing of the skin. Fostex Cream is approximately twice as drying as Fostex Cake.

Fostex Cream is also used as a therapeutic shampoo in dandruff and oily scalp.

Write for samples.

WESTWOOD PHARMACEUTICALS • Buffalo 13, New York


I know I can
count on it
a reservoir of dependable performance
Terramycin® therapy
BRAND OF OXYTETRACYCLINE

a reservoir of dependable performance– Terramycin® therapy

today's pediatric *forms of Terramycin*

Cosa-Terrabon®

OXYTETRACYCLINE WITH GLUCOSAMINE

ORAL SUSPENSION / PEDIATRIC DROPS

delicious fruit-flavored aqueous suspensions preconstituted for convenience and economy

Science for the world's well-being™

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

Cosa-Terrabon provides oxytetracycline (Terramycin®) with glucosamine for enhanced absorption. Because Cosa-Terrabon is preconstituted, stable, and unusually well accepted by children, waste of medication is largely avoided. The dependability of Cosa-Terrabon derives from the broad antimicrobial effectiveness, excellent toleration, and low order of toxicity of oxytetracycline.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (e.g., amebae, pinworms), Cosa-Terrabon is indicated in a great variety of pediatric infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: For infants and children, 10 to 20 mg. of Terramycin per pound of body weight daily, in divided doses, is usually effective.

wt. lbs.	daily dosage (10 mg./lb.)	practical daily dosage	
		Oral Suspension 125 mg./tsp.	Pediatric Drops 5 mg./drop
10	100 mg.	—	5 gtt. q.i.d.
20	200 mg.	½ tsp. q.i.d.	10 gtt. q.i.d.
30	300 mg.	½ tsp. t.i.d. and 1 tsp. h.s.	15 gtt. q.i.d.
40-50	400-500 mg.	1 tsp. q.i.d.	—
60	600 mg.	1 tsp. t.i.d. and 2 tsp. h.s.	—

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms—particularly monilia and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terrabon Oral Suspension*—125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; and *Cosa-Terrabon Pediatric Drops*—5 mg. per drop (100 mg. per cc.), 10 cc. bottle with calibrated plastic dropper. Terramycin is also available as *Cosa-Terramycin® Capsules*, 250 mg. and 125 mg.; and as *Terramycin Intramuscular Solution, conveniently preconstituted*, in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.

NEW

rich, creamy lather
with improved

LOWILA® CAKE

Cleans tender or dermatitic skin without irritation.
Lowila Cake does not contain any irritating ingredients of soap, such as alkali, fatty acids or perfumes. Lowila Cake maintains healthy skin pH and aids healing.

Contains sodium lauryl sulfoacetate in a corn dextrin base, acidified with lactic acid.

Write for samples.

WESTWOOD PHARMACEUTICALS
Buffalo 13, New York

Now, for the first time...

the premature infant can maintain his own constant body temperature indefinitely . . . the new

Infant Servo-Controller for the Isolette®

provides automatic body-temperature control until the natural thermoregulatory mechanism can mature and take over

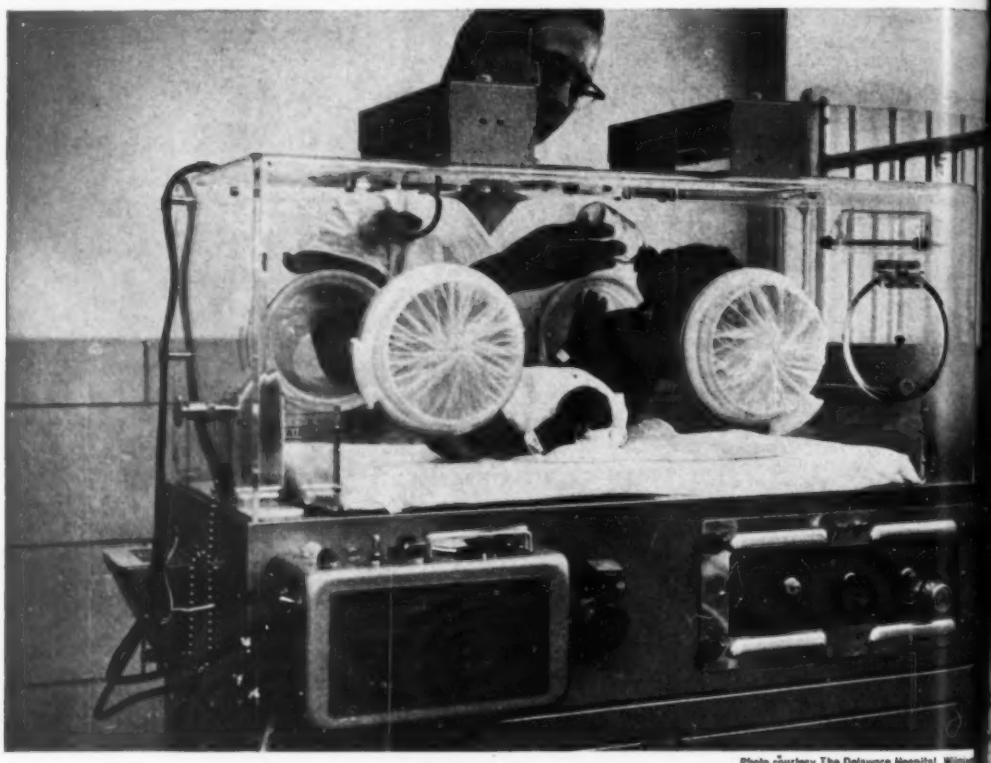


Photo courtesy The Delaware Hospital, Wilmington

With the new INFANT SERVO-CONTROLLER for the ISOLETTE® the premature infant acts as his own thermostat. Changes in the baby's skin temperature control the on-off cycling of low-intensity infra-red lamps thus providing—

- **gentle, radiant heat** — when demanded by a fall in the infant's skin temperature.
- **minute-to-minute, stable control** — of even the tiniest infant's body temperature at any preset level within ±0.5°F.
- **utmost safety**—instantaneous response to the temperature-sensing element, taped to the baby's abdomen, turns off the lamps the moment the preset body temperature is reached.

An electronic safety thermostat provides an additional safeguard to protect the infant. As soon as the body temperature rises above the preset point, this secondary heat-sensing element turns off the lamps, sounds a buzzer and lights a red warning lamp.

The new INFANT SERVO-CONTROLLER is easy to operate. It can be factory-adapted to any ISOLETTE incubator, or you may purchase the new model C-77 ISOLETTE with the INFANT SERVO-CONTROLLER already in place.

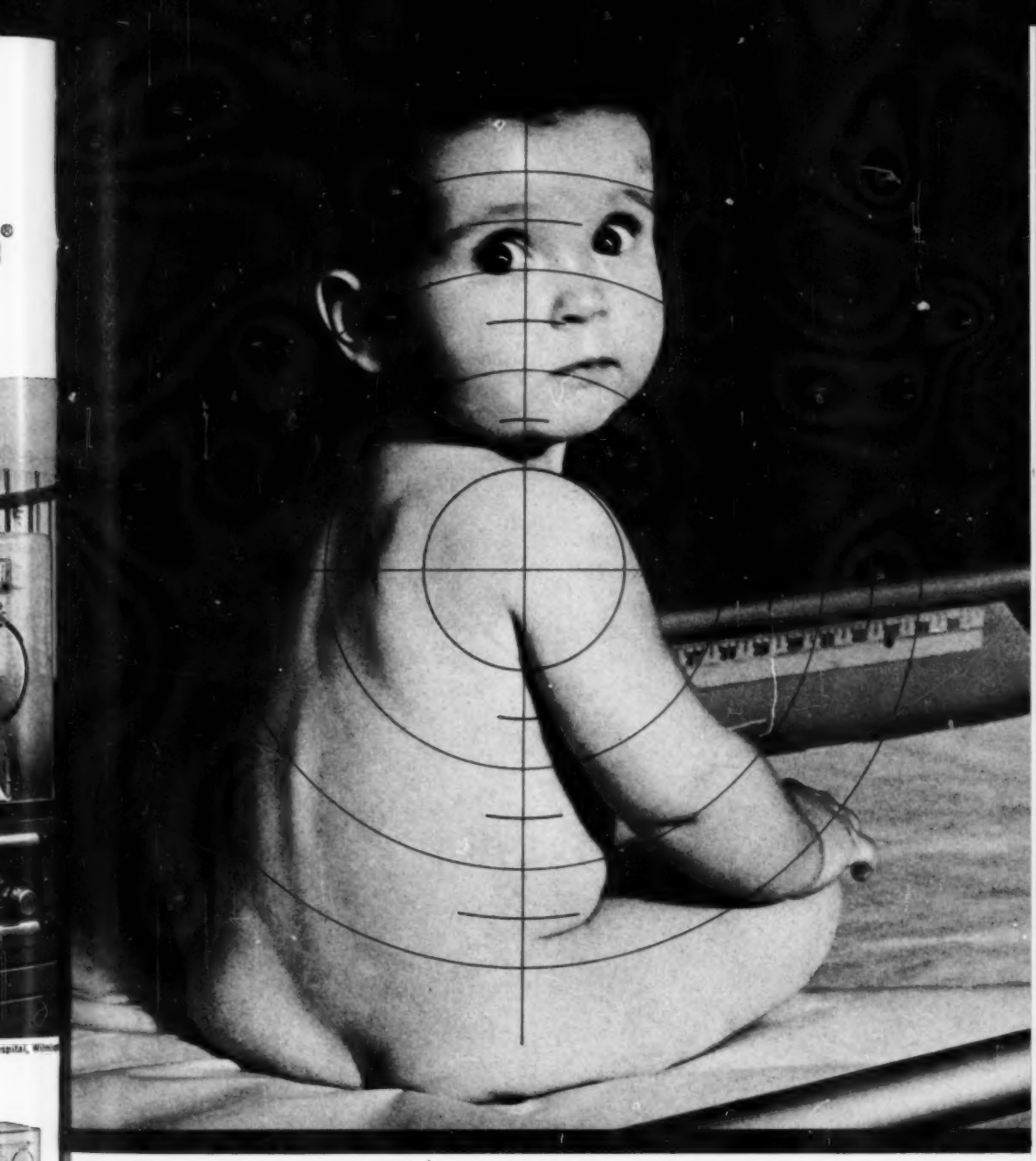
The **Isolette** incubator alone continues to provide optimal isolation and precise, constant, fully-automatic control of temperature, humidity and oxygen—factors vital for survival of premature infants.

For additional information write, or phone collect from any point in the U.S.A.

AIR-SHIELDS, INC.

Hatboro, Pa. OSborne 5-5200

Leaders in electronic research and engineering to serve medicine



Target for Dermatoses

A baby's skin—without the protection of an adequate "acid mantle"—is an easy target for inflammation, infection, and stubborn chronic dermatoses.

COR-TAR-QUIN™ is for babies—and for any patient in whom low resistance, refractoriness to treatment, or risk of complications puts a premium on fast, dependable response.

Thoroughly established in dermatologic practice, COR-TAR-QUIN is one of the most sophisticated topical preparations available today . . . a unique combination of anti-inflammatory hydrocortisone, anti-infective diiodohydroxyquinoline, and keratolytic tar incorporated in the exclusive ACID MANTLE® vehicle that potentiates active ingredients and speeds healing by restoring and maintaining the protective mantle of acidity characteristic of healthy skin.

COR-TAR-QUIN™

CREME pH 5.0 **LOTION**

1% diiodohydroxyquinoline with ¼%, ½% or 1% micronized hydrocortisone alcohol and 2% liquor carbonis detergens in the exclusive ACID MANTLE® vehicle.

DOME

WORLD LEADER IN DERMATOLOGICALS

DOME CHEMICALS INC.

New York · Los Angeles

take the
tears and tantrums
out of
"nose-drop time"

Tyzine®

brand of tetrahydrozoline hydrochloride (0.05%)

pediatric nasal drops

specifically formulated for children

Science for the world's well-being™

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

TYZINE is tetrahydrozoline hydrochloride, a sympathomimetic amine providing almost immediate relief of nasal congestion that lasts up to 6 hours after a single administration. TYZINE is odorless and tasteless, virtually free of sting or burn, and rebound congestion. TYZINE does not impair ciliary activity and is physiologically buffered to pH 5.5. These are qualities of an ideal nasal decongestant.

INDICATIONS: For relief of inflammatory hyperemia and edema of the nasal mucosa and congestive obstruction of sinus and eustachian ostia, as may occur in the common cold, hay fever, perennial vasomotor rhinitis, chronic hypertrophic rhinitis, and sinusitis.

DOSAGE AND ADMINISTRATION: Infants under 2 years—1 or 2 drops. *Children 2 to 6 years*—2 or 3 drops. Instill in each nostril as needed, not more often than every three hours.

SIDE EFFECTS: Transient mild local irritation after instillation has been reported in rare instances.

PRECAUTIONS: Always use the 0.05% pediatric strength for infants and younger children. The 0.1% concentration of TYZINE should be restricted to adults and children 6 years and over. Avoid doses greater or more frequent than those recommended above. Use with caution in hypertensive and hyperthyroid patients. Overdosage may cause drowsiness, deep sleep, and, rarely, marked hypotension in infants and young children: KEEP OUT OF HANDS OF CHILDREN OF ALL AGES.

SUPPLIED: TYZINE *Pediatric Nasal Drops,* ½-oz. bottles, 0.05%, with calibrated dropper. Also available: TYZINE *Nasal Solution,* 1-oz. dropper bottles, 0.1%. TYZINE *Nasal Spray,* 15 cc., in plastic bottles, 0.1%.

More detailed professional information available on request.

FOR ASTHMA, EMPHYSEMA, CHRONIC BRONCHITIS

INSPIRED RELIEF IN SECONDS[1]

VAPONEFRIN®

A TEXTBOOK THERAPY FOR ASTHMA

Just 3 to 6 inhalations of Vaponefrin relieve bronchospasm and restore breathing comfort

"...the greatest improvement (in vital capacity-time relationship) occurs during the first second."[1]

Unsurpassed record of efficacy and safety Vaponefrin Solution (racemic epinephrine)...

- "The preparation we have found most effective is called 'Vaponefrin'."[3]
- "The deposition of a fine bronchodilator mist [such as Vaponefrin] on the mucosa of the bronchi and bronchioles of the respiratory tract presents many significant advantages over the parenteral use of epinephrine."[4]
- May be used by hypertensive and cardiac patients; no appreciable effects on blood pressure, peripheral resistance, C.N.S., with ordinary doses.[2]

Produces particles of critical micrometric accuracy, for maximum efficacy Vaponefrin Nebulizer...

- Its exclusive baffle produces a voluminous mist of particles with average radii of 1 micron.[1]
- Only particles in this range can penetrate smaller bronchioles and alveoli for almost instantaneous effect.[1]

Professional literature and a complimentary office demonstration set available on request.

Supplied: *Solution (2.25%) racemic epinephrine hydrochloride, bottles of 7.5, 15 or 30 cc.; Nebulizers, Standard size and conveniently-carried Pocket size. Also Vaponefrin Aerosol Unit (Nebulizer and Solution).*

References:

1. Segal, M. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema. New York, Grune & Stratton, 1953, p. 99. 2. Forbat, S. M., and Wilson, R. H. L.: Ann. Int. Med. 50:1241, 1959. 3. Baroch, A. L., and Cromwell, H. A.: Med. Clin. No. America, May 1940, p. 621. 4. Bickerman, H. A., and Baroch, A. L.: Drugs of Choice, 1960-1961 (W. Modell, ed.), St. Louis, The C. V. Mosby Co., 1960, p. 523.

The VAPONEFRIN Company
666 Fifth Avenue • New York 19, N.Y.

Documented by 163 published clinical evaluations and standard textbook references.

NEVER SKIPS HER
VIFORT®
(Aqueous Polyvitamin) DROPS
• completely water-dispersed... including vitamins A and D
• 3 to 5 times better absorbed, utilized, and stored than from oily media
• deliciously orange-flavored ... a treat for infants and growing children
• backed by years of clinical study and pediatric application
Dosage: 0.3 to 0.6 cc. daily; may be placed directly on tongue or taken in fruit juices or milk.
Supplied: Bottles of 15, 30, and 60 cc. with graduated dropper.
Also available: VIFORT Capsules, bottles of 30 and 100.
Endo®
Samples? Literature? Write—
ENDO LABORATORIES, Richmond Hill 18, New York

B.A.C.

For the Prevention and Treatment of Recurring Upper Respiratory Infections and Infectious Asthma

B.A.C.—Acellular Bacterial Antigen Complex—although derived from bacteria, is not a cellular vaccine. Prepared by the special Hoffmann process of coprecipitation, it provides the specific protective substances of the bacterial cell *plus* the toxins and metabolites. Standardized to uniform potency, B.A.C. is an acellular, water-clear solution, essentially free of sensitizing extraneous components, and is not liable to deterioration on keeping, with resultant loss of antigenic properties.

B.A.C. avoids the pitfalls of antibiotic therapy—Stimulates immune body formation, avoids development of resistant bacteria and superinfections and liability to allergic reactions.

B.A.C. provides important antigens lacking in cellular vaccines—Vaccines lack important specific surface antigenic factors and are deficient in exotoxins and other antigenic metabolites.

B.A.C. combines the essential immunogenic factors for maximum immunologic response.

B.A.C. acts to improve the natural defense mechanisms—The action of B.A.C. is immunologically natural, namely, stimulation of the host's defense against bacterial invaders.

B.A.C. affords prompt, effective and safe therapy—Controlled clinical studies[1-5] in both children and adults have consistently shown favorable response in more than 80 per cent of cases of upper respiratory infection and infectious asthma. Significant side effects have been rarely noted and are eliminated by dilution of the antigen.

B.A.C. is available in multiple dose vials in several different combinations for broad-spectrum immunization. Complete information on B.A.C. preparations, clinical experience, and dosage will be supplied on request.

1. Spielman, A. D.: New York J. Med. *55*:1603 (June 1) 1955.
2. Shinefield, M. A.: New York J. Med. *56*:1466 (May 1) 1956.
3. Dalven, J., and Romano, F. J.: New York J. Med. *57*:1748 (May 15) 1957.
4. Gundy, J. E.: J. Pediat. *51*:516 (Nov.) 1957.
5. Spielman, A. D.: A.M.A. Arch. Otolaryng. *67*:204 (Feb.) 1958.

Hoffmann Laboratories, Inc.
666 Broadway, Paterson 4, N. J.

Child Life SHOES provide

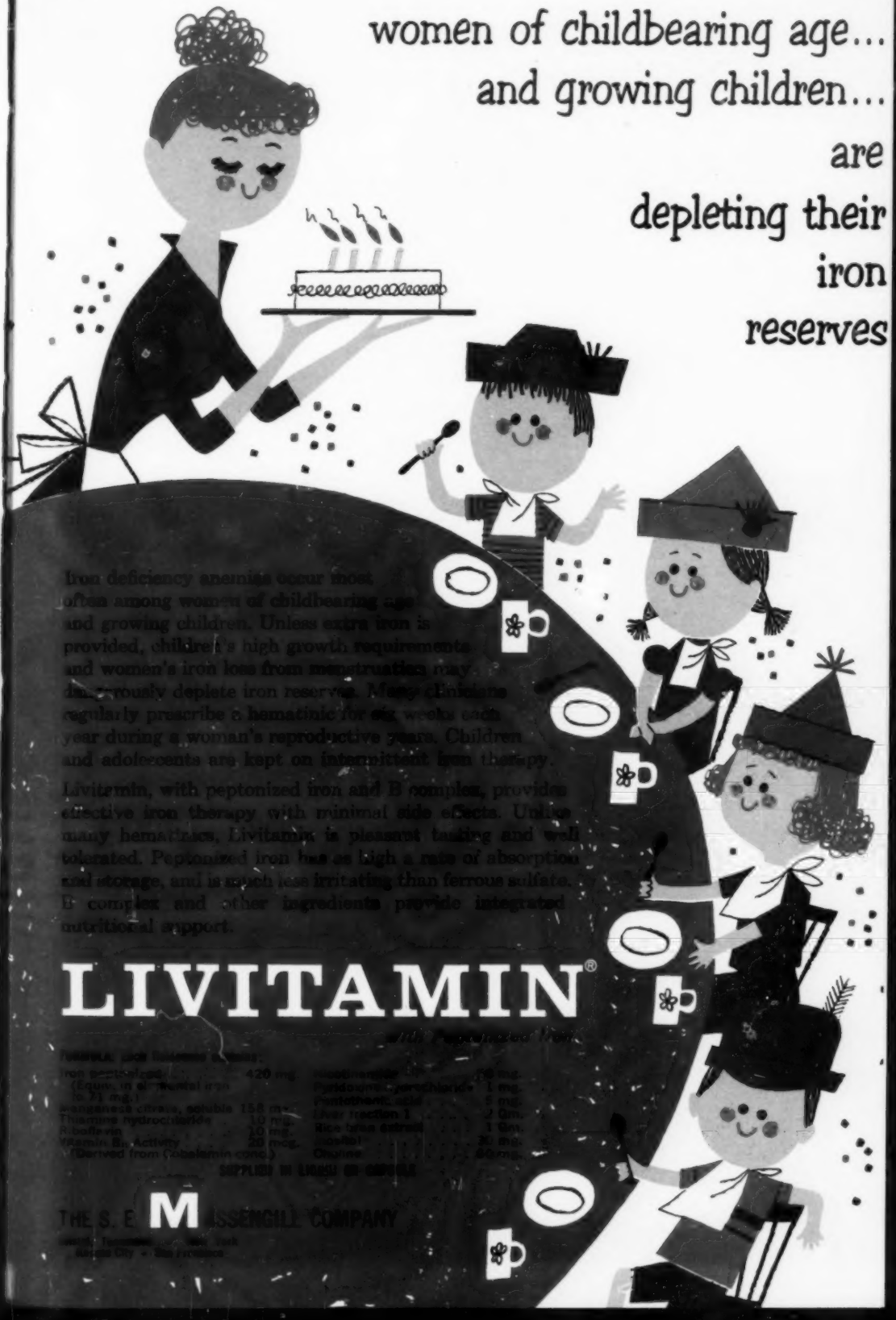
Winged Mismate Service

When mismated shoes are needed, they are needed NOW — not two or three weeks hence. The sooner the shoes arrive, the better for your patient. Because this is so true — and human comfort is important — CHILD LIFE gives special priority to Mismate Service. In nine cases out of ten, shoes are shipped the same day the order is received . . . and they are sent *special delivery* parcel post.

As a physician, it's good to know that this brand of service backs up your recommendations to mothers. And it's good to know, too, that CHILD LIFE Mismate Service carries only a very nominal premium in price. The CHILD LIFE dealer in your community — selected for his special knowledge of children's shoes — will be glad to fill you in on all details. Please write for his name.

Or if you prefer to write direct for information, your inquiry will be welcome and promptly acknowledged.

HERBST SHOE MANUFACTURING COMPANY
MILWAUKEE 45, WISCONSIN


women of childbearing age...
and growing children...
are
depleting their
iron
reserves
Iron deficiency anemias occur most often among women of childbearing age and growing children. Unless extra iron is provided, children's high growth requirements and women's iron loss from menstruation may dangerously deplete iron reserves. Many clinicians regularly prescribe a hematinic for six weeks each year during a woman's reproductive years. Children and adolescents are kept on intermittent iron therapy.
Livitamin, with peptonized iron and B complex, provides effective iron therapy with minimal side effects. Unlike many hematinics, Livitamin is pleasant tasting and well tolerated. Peptonized iron has as high a rate of absorption and storage, and is much less irritating than ferrous sulfate. B complex and other ingredients provide integrated nutritional support.
LIVITAMIN®
with Peptonized Iron
THE S. E. MASSENGILL COMPANY

LIVITAMIN® *with Peptonized Iron*

. . . the preferred hematinic

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

THE S. E. MASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco

NOW—a new mouth-fitting nipple designed to reduce feeding problems

New Curity Rib Nipple helps prevent excessive air swallowing– won't collapse or bite shut

CURITY Rib Nipple fills out mouth from corner to corner—Hollow side ribs seal out air, assure steady milk flow. Won't bite shut, even under hard sucking and biting.

Now, for the first time in the history of modern baby care, a nipple has been made to fit the mouth completely—from corner to corner.

The *Curity* Rib Nipple, with its reinforced side channels, fills out an area that the regular bell-shaped nipple leaves open to air swallowing.

The Rib Nipple has been tested for two years in hospital trials. Tests on sluggish eaters, premature babies and cleft palate cases showed a marked improvement in eating habits. Subsequent trials in the home showed that mothers preferred the Rib Nipple 2 to 1 over regular nipples.

Milk always gets through

Feeding is steadier, faster, easier. The strong, supple rubber of the *Curity* Rib Nipple can withstand sterilizing and detergent action to an exceptional degree. In laboratory tests, the *Curity* Rib Nipple lasted twice as long as the leading nipple of conventional design.

Available in complete Sure-Grip nurser. New contoured Curity *bottle provides exceptionally firm grip. Square shape stores easy.*

Curity®

Rib Nipple

THE KENDALL COMPANY
BAUER & BLACK
DIVISION

Today's little "limey"

needs a half barrel of orange juice his first two years

The British navy once conquered scurvy by giving its sailors lime juice to drink, but the problem has cropped up again today in an unexpected place: among infants! Noting a "recent and alarming prevalence" of infant scurvy, Whelan and coworkers state: "Emphatic and more specific advice from doctors concerning the value of orange juice in infant nutrition . . ." is needed.[1]

The infant should be given, during the first two years of his life, a total of 2,106 ounces—a half barrel—of orange juice. Whelan's group specifically recommends that . . . "Starting at two weeks of age, infants should receive, daily, one teaspoonful of orange juice (fresh, frozen or canned) diluted with an equal amount of boiled water. The amount should be increased by one teaspoonful of each, twice weekly, until the baby is receiving one ounce of orange juice and one ounce of water. Thereafter continue to increase the orange juice at the same rate until, at two months of age, the infant is receiving two ounces of orange juice (diluted with one ounce of water). At one year of age the orange juice should be increased to three or four ounces daily."

It's easy to be on the safe side. Check with each mother to be sure she's doing her part to help her infant empty that half barrel of orange juice he needs . . . Florida orange juice, of course! — fresh, frozen, canned, or in cartons.

1. Whelan, W. S.; Fraser, D.; Robertson, E. C., and Tomczak, H.: Canad. M.A.J. *78*:177 (Feb. 1) 1958.

©Florida Citrus Commission, Lakeland, Florida

Children are happier when doctors choose Fleet® Enema

They are more willing to accept this ready-to-use pediatric enema because they are spared the ordeal of complicated old-style procedures. The compact Fleet Enema takes less than a minute to give and avoids the discomfort of large volumes of liquid. Insertion is made easy and safe because of the *pre-lubricated, anatomically correct* 2-inch rectal tube.[1] Fleet Enema can be prescribed with confidence as "a safe and effective enema preparation for even small children."[2]

Widely useful for a variety of diagnostic and therapeutic purposes—even for your patients on sodium-restricted regimens.[3] Systemic absorption is negligible.[2,3]

Pediatric size, 2¼ fl.oz. *Regular size,* 4½ fl.oz. *100 cc. contains:* 16 Gm. sodium biphosphate and 6 Gm. sodium phosphate. *Also available:* Fleet Oil Retention Enema, 4¼-fl.oz. ready-to-use unit containing Mineral Oil U.S.P.

READY-TO-USE SQUEEZE BOTTLE

Fleet® FLEET® ENEMA PEDIATRIC

1. Frech, H. C., and Lanier, L. R., Jr.: Am. J. Obst. & Gynec. 74:1146, 1957. 2. Way, W. G., et al.: Virginia M. Month. 85:291, 1958. 3. Hellman, L. D.: To be published.

C. B. FLEET CO., INC. LYNCHBURG, VIRGINIA

MODILAC

A NEW PREPARED MILK FORMULA FOR MORE EFFICIENT NOURISHMENT

Looks and tastes like milk... offers nourishment comparable to that received by infants who are successfully breast fed. Immediately acceptable to the newborn, it helps the infant make an easy transition to fresh milk later.

Excellent protein and calorie utilization. A recent clinical study[1] indicated that infants receiving Modilac, in general, performed more efficiently than those of the control groups; weight increment from 2 to 16 weeks was highest; weight gain *per unit* of protein or *per calorie* consumed was greatest.

Modilac is "flash-sterilized." Browning and caramelization, the result of amino-sugar bonding and prolonged high processing temperatures, are markedly reduced. Destruction of heat-labile amino acids and vitamins is minimized.

The carbohydrate modifier in Modilac is high in dextrins, low in reducing sugars . . . provides "spaced" CHO assimilation.

Corn oil replaces butterfat, helps to maintain linoleic acid blood serum levels comparable to those of breast fed infants . . . assures optimal caloric efficiency.[2] Added vitamins A, C, D, B_6 and thiamine appropriately supplement the natural vitamin content.

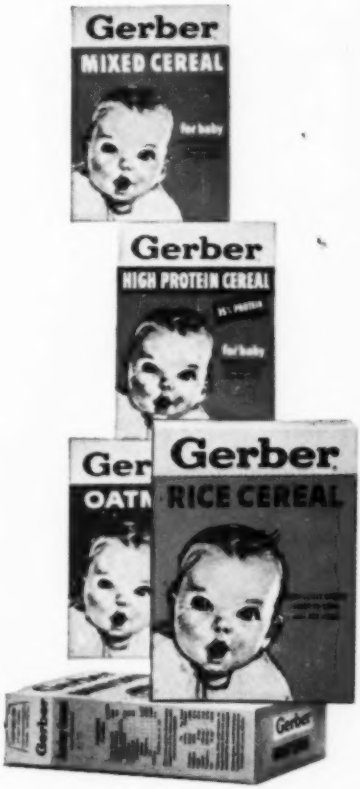
GERBER® BABY FOODS FREMONT MICHIGAN

BABIES ARE OUR BUSINESS... OUR ONLY BUSINESS!®

1. Mosovich, Luis L., Pessin, Vivian and Lowe, Charles U.; Effects of Milk Composition on Baby Composition, AM. J. Dis. Child. **100**: 791-792, 1960.
2. Adam, Doris J. D., Hansen, Arild E. and Wiese, Hilda F.; Essential Fatty Acids in Infant Nutrition, J. Nutrition **66**: 555-564, 1958.

GERBER BABY CEREALS

SPECIALLY PREPARED FOR NEEDED IRON AND THIAMINE



When you recommend cereal for your baby patients, you'll find Gerber Cereals provide several nutritional benefits.

First, iron assimilation is assured. Gerber's exclusive cereal formulation contains a selected form of iron (sodium iron pyrophosphate) which is as easily absorbed, and to the same degree, as the iron found in natural sources.* One-half ounce (6 tablespoons) provides 7 mg. or 100% of the Recommended Daily Dietary Allowance for infants and young children.

Second, all Gerber Cereals are enriched with the B-vitamins, thiamine, riboflavin and niacin.

Third, they supply appetite satisfaction and extra calories.

Last, digestibility is assured. Gerber Cereals are thoroughly pre-cooked for ready digestibility. Because of this easy digestibility, they can be offered to the infant as soon as solid food is indicated. 5 varieties—with Rice Cereal and Barley Cereal, recommended as starters because they're one-grain and hypo-allergenic.

BABIES ARE OUR BUSINESS...OUR ONLY BUSINESS!®

GERBER® BABY FOODS FREMONT MICHIGAN

*A.M.A. Journal of Diseases of Children, 95:109-119, 1958

on the pathogenesis of pyelonephritis

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."[1]

Recent experimental evidence in animals strongly supports the view that obstruction of the tubules in the medulla, as opposed to the cortex, predisposes the kidney to pyelonephritis,[2] and ". . . as few as 10 organisms injected into the medulla were capable of causing infection."[3]

The "exquisite sensitivity"[4] of the medulla to infection highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."[5]

An agent, such as FURADANTIN, which has a specific affinity for the urinary tract and which is actively excreted by the cells of the tubules, as well as of the glomeruli,[6] is particularly suited to meet the problems posed by the pathogenesis of pyelonephritis and the primary pathways of infection.

in pyelonephritis

to eradicate the pathogens

no matter the pathway

FURADANTIN®

brand of nitrofurantoin

high urinary concentration

glomerular filtration

tubular excretion

effective at glomerular and tubular levels: In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

rapid antibacterial action: Antibacterial concentrations of FURADANTIN are in the urine in 30 minutes.

broad bactericidal spectrum: FURADANTIN is bactericidal against a wide range of gram-positive and gram-negative bacteria including certain organisms resistant to other agents.

free from resistance problems: Development of bacterial resistance to FURADANTIN has not been a problem in over 8 years of extensive clinical use.

well tolerated—even after prolonged use: FURADANTIN is nontoxic to kidneys, liver and blood-forming organs. No monilial superinfection, staphylococcic enteritis, proctitis or anovulvar pruritus has ever been reported.

no cross resistance or cross sensitization with other drugs: FURADANTIN, a synthetic nitrofuran, is unrelated chemically to any other class of antimicrobial drugs; cross resistance or cross sensitization does not occur.

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d. with meals and with food or milk on retiring. **SUPPLIED:** Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Schreiner, G. E., A.M.A. Arch. Int. M. **102**:32, 1958. 2. Rocha, H., et al.: Yale J. Biol. & Med. **32**:120, 1959. 3. Freedman, L. R.: Yale J. Biol. & Med. **32**:272, 1960. 4. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. **30**:406, 1958. 5. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958. 6. Paul, M. F., et al.: Am. J. Physiol. **197**:580, 1959.

NITROFURANS—a *unique* class of antimicrobials

EATON LABORATORIES, DIVISION OF THE NORWICH PHARMACAL COMPANY

NORWICH, NEW YORK

there hardly seems an excuse for having a runny nose these days

The youngster who stops sniffling and begins breathing freely in a few minutes with all air passages cleared...and no sense of jitteriness or nasal irritation...is experiencing the Novahistine Effect.

Each 5 cc. teaspoonful of good-tasting Novahistine Elixir contains: phenylephrine HCl, 5.0 mg. and prophenpyridamine maleate, 12.5 mg. And the distinctly additive action achieved by combining this orally effective vasoconstrictor and superior antihistamine usually controls cold symptoms better than any single drug.

PM

Novahistine® Elixir

PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc., Indianapolis 6, Indiana

because

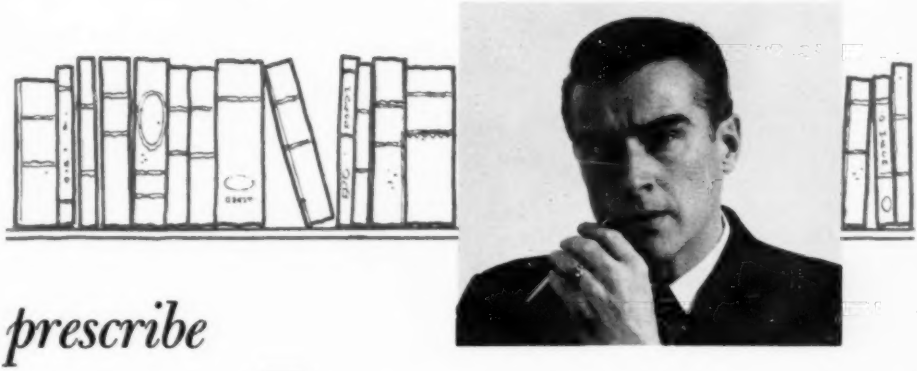
there is a record of risk in iron therapy

"In recent years the serious pathologic effects of an overload of iron on structure and function of organs have received much attention."

Schulman, I.: Pediatrics 18:299, Aug., 1956.

"In a three year period in New York City, over 40 cases of acute iron poisoning in children were reported to the Poison Control Center . . . The death rate from this form of intoxication is far higher than from acetylsalicylic acid."

Sisson, T. R. C.: Quart. Rev. Pediat. 15:47, Jan.-Mar., 1960.



prescribe

CHĒL-IRON®

Brand of Ferrocholinate*

for effectiveness with safety because of chelation

Clinically confirmed as an effective hematinic[1] . . . yet *chelation* provides a built-in molecular barrier against g.i. intolerance and systemic toxicity.[1,2]

For pediatric patients . . . CHĒL-IRON Pediatric Drops and CHĒL-IRON Liquid taste good (no astringency) . . . won't stain teeth . . . can be mixed in formula, milk, or juice without precipitation . . . or taken on an empty stomach without intolerance.

And equally important, since accidental iron poisoning in children is a growing problem[3]—CHĒL-IRON Tablets prescribed for adults are safe to have around the house because of *chelation.*

CHĒL-IRON *Pediatric Drops:* Equiv. 25 mg. elemental iron per cc. Bottles of 60 cc. with calibrated dropper. CHĒL-IRON *Liquid:* For children past the "drop-dose" stage—equiv. 50 mg. elemental iron per teaspoonful. Bottles of 8 fl. oz. CHĒL-IRON *Tablets:* For older children and adults—each tablet equiv. 40 mg. elemental iron. Bottles of 100.

Also available: CHĒL-IRON PLUS *Tablets:* Chelated iron plus B_{12}, other B vitamins and C. Bottles of 100.

1. Franklin, M., et al.: J.A.M.A. 166:1685, Apr. 5, 1958. 2. A.M.A. Council on Drugs: J.A.M.A. 171:891, Oct. 17, 1959. 3. A.M.A. Committee on Toxicology: J.A.M.A. 170:676, June 6, 1959.

*U.S. Pat. 2,575,611

KINNEY & COMPANY, INC.
Columbus, Indiana

because

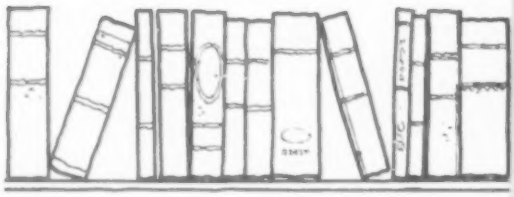
there is a record of risk in antiemetic therapy...

"Functional vomiting should be carefully distinguished from organic vomiting. Grave consequences may follow if evidences of organic derangement, such as tumors or acute conditions requiring surgical therapy, are masked by treatment designed to control vomiting alone."

Bradley, J. E.: Mod. Med. 20:71, Oct. 15, 1952.

"Phenothiazine tranquilizers should therefore not be prescribed indiscriminately for the symptomatic treatment of nausea and vomiting in childhood."

Cohlan, S. Q.: GP 21:136, Feb., 1960.



prescribe

EMETROL®

Phosphorated Carbohydrate Solution

for effectiveness with safety because of physiologic action

Effective in most cases of *functional* vomiting, often with the first dose[1] . . . yet because its action is *entirely physiologic,* EMETROL will not mask organic pathology[2] or expose the patient to hazardous drug side effects. Always a wise first choice for children . . . especially useful in the "g.i. virus" season.

Dosage: 1 or 2 teaspoonfuls for children, 1 or 2 tablespoonfuls for adults, repeated at 15-minute intervals as required. DO NOT DILUTE or drink fluids immediately before or after each dose.

Supplied: Bottles of 3 and 16 fl. oz.

1. Bradley, J. E., et al.: J. Pediat. 38:41, Jan., 1951. 2. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, Apr., 1954.

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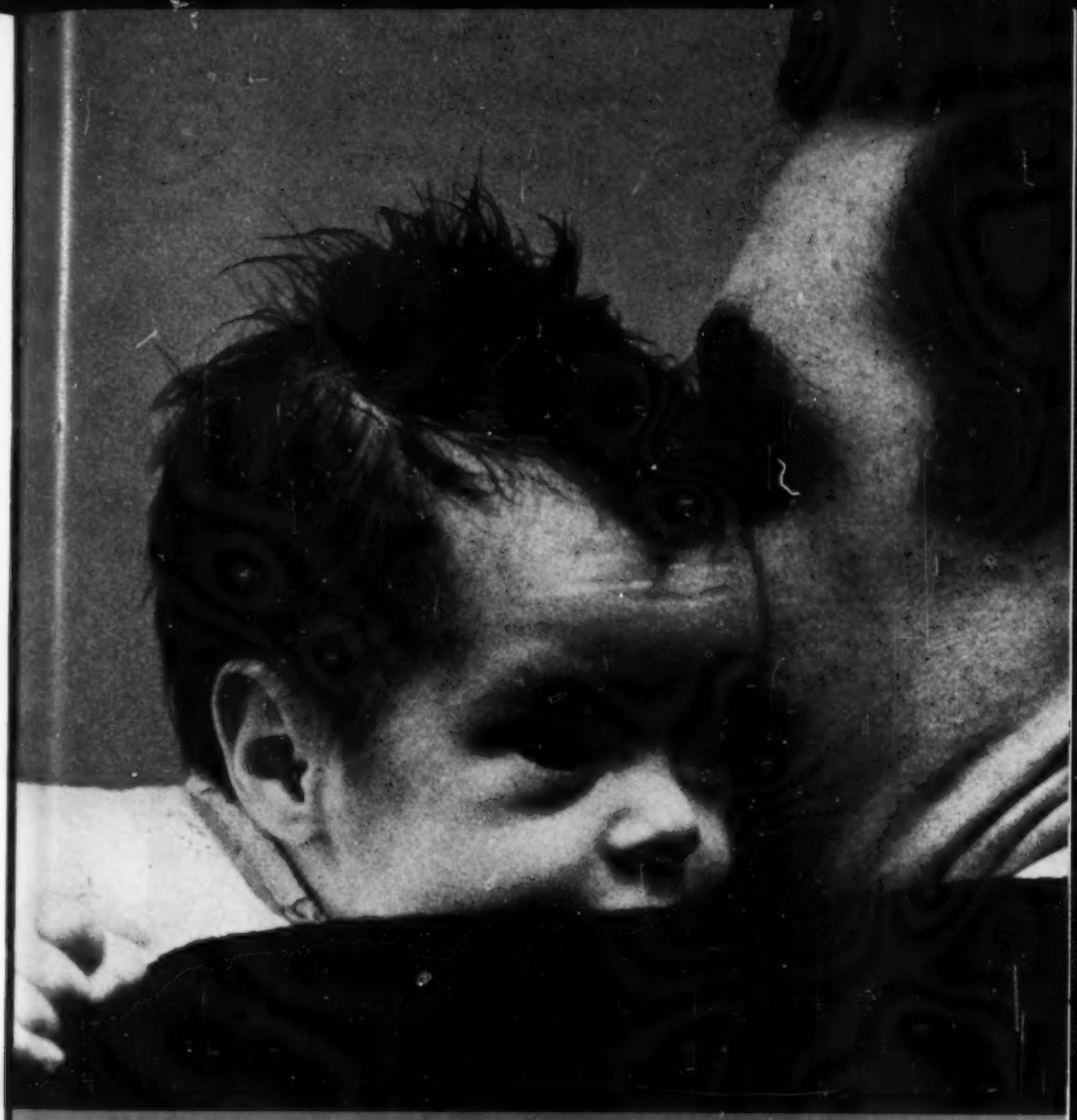


HELPING PREVENT IRON DEFICIENCY ANEMIA FOR A QUARTER OF A CENTURY: Baker's MODIFIED MILK

Iron deficiency anemia in infants continues to be a major health problem. It has been shown that milk is an excellent vehicle for iron administration:[1,2]

- absorption is high;
- satisfactory hemoglobin responses are demonstrated;
- digestive disturbances are minimized.

That is why Baker's Modified Milk provides iron (7.5 mg per quart at 1:1 dilution). The Baker Laboratories, Inc., Cleveland 3, Ohio.

OPTIMUM NUTRITION: Providing all the normal dietary requirements plus a reserve for stress situations.

1. Schulz, Jeannette & Smith, N. J.: A.M.A. J. Dis. Child. 93:109 (1956).
2. Josephs, H.W.: Medicine 32:125 (1953).

treat your little patients to good-tasting Mysteclin-F

provides tetracycline effectiveness and protection against monilial superinfection

Mysteclin-F is phosphate-potentiated tetracycline, combined with Fungizone, the new highly active antifungal agent. It provides broad spectrum effectiveness in a wide range of bacterial infections plus protection against monilial superinfection (Candida Albicans) often associated with antibiotic therapy. A delicious mixed fruit-flavored preparation, Mysteclin-F provides enhanced stability.

Supplied: *Mysteclin-F For Syrup*—125 mg. phosphate-potentiated tetracycline (HCl equivalent) and 25 mg. amphotericin B (Fungizone) per 5 cc. teaspoonful. *Mysteclin-F For Aqueous Drops*—100 mg. phosphate-potentiated tetracycline (HCl equivalent) and 20 mg. amphotericin B (Fungizone) per cc. For complete information, consult package circular or write to The Professional Service Department, Squibb, 745 Fifth Ave., New York 22, New York.

'MYSTECLIN'® AND 'FUNGIZONE'® ARE SQUIBB TRADEMARKS.

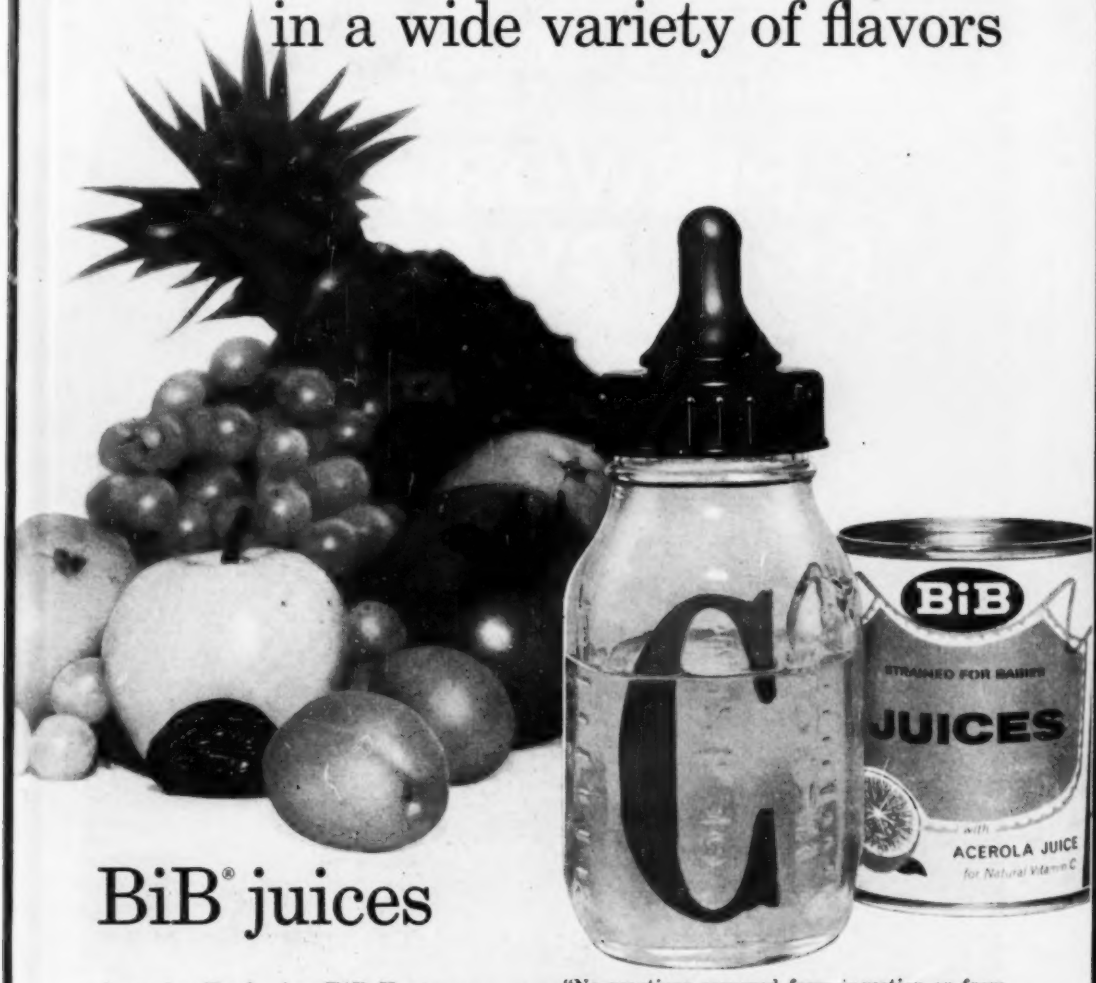
MYSTECLIN-F

Squibb phosphate-potentiated tetracycline with amphotericin B (Fungizone)

for syrup / for aqueous drops

SQUIBB

NOW...high natural vitamin C in a wide variety of flavors



BiB® juices

Acerola–Exclusive BiB Feature:

All BiB juices—Orange, Apple, White Grape, Pineapple, Prune-Orange, Orange-Apricot, and Tomato—are standardized to protective vitamin C levels with Acerola, the richest known *natural* source of vitamin C.[1,2] Each ounce of *all* BiB juices—citrus or non-citrus—provides more than the minimum daily requirement of vitamin C for infants.

BiB Orange Juice–Hypoallergenic

Hypoallergenicity and improved tolerance are achieved through special processing which reduces seed protein and peel oil impurities to negligible quantities. In a clinical study with Acerola, "No reactions occurred from ingestion or from skin and intradermal tests with Acerola juice."[2]

A Wide Variety at an Early Age

BiB juices permit early introduction of a wide variety of flavors—valuable in taste-training the infant. Special process assures free flow through bottle nipple; ideal for spoon or cup feeding, too. BiB juices require no reconstitution, no heating, no defrosting. All mother does is open the can of BiB juice and it's ready for feeding.

References: (1) Asenjo, C. F., and Freire de Guzman, A. R.: Science *103*:219 (Feb. 22) 1946. (2) Clein, W. H.: J. Pediat. *48*:140-145 (Feb.) 1956.

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Without staining • vomiting • enemas
nausea • fasting • laxatives

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'ANTEPAR' SYRUP Piperazine Citrate, 100 mg. per cc.

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Literature and patient instruction sheets available on request

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liquid analgesic-antipyretic, exceptionally well adapted for pediatric use

Liquiprin* for children

convenient liquid form

and calibrated dropper facilitate accurate dosage and administration—no tablets to break, crush, or dissolve

pleasant taste

assures acceptance by young patients—also mixes readily with fruit juice, milk, or formula

unique safety bottle

valve inside bottle prevents children from drinking or pouring contents—even when cap is off

- EFFECTIVE ANALGESIC AND ANTIPYRETIC[1-6]
- CLINICALLY EFFECTIVE FOR FEVER IN INFANTS AND CHILDREN[1]
- PARTICULARLY USEFUL FOLLOWING IMMUNIZATIONS
- SAFE, WELL TOLERATED FOR CONTINUED USE[1,5,7,8]
- NOT CONVERTED TO SALICYLATE[3,5,9,10]...CAN REPLACE ASPIRIN IN PATIENTS ALLERGIC TO LATTER[2,7,8]
- PRODUCES LESS IRRITATION THAN ASPIRIN...BETTER TOLERATED[3,5-8,10,11]
- NOTABLY FREE OF TINNITUS, GIDDINESS AND LISTLESSNESS[10]
- HAS NEGLIGIBLE EFFECT ON PROTHROMBIN TIME[5,10]

LIQUIPRIN Salicylamide Suspension contains 1 gr. salicylamide per cc. Recommended dosage: ½ dropper (1¼ gr.) for each year of age, not to exceed 2 droppers (5 gr.). Dosage may be repeated every 3 to 4 hours if necessary. Bottles of 50 cc.

References: (1) Vignec, A. J., and Gasparik, M.: J.A.M.A. 167:1821 (Aug. 9) 1958. (2) Current Concepts in Therapy: New England J. Med. 257:513 (Sept. 12), 1957. (3) Smith, P. K., in Drill, V. A.: Pharmacology in Medicine, New York, McGraw-Hill Book Company, Inc., 1954, pp. 20/16, 20/17. (4) Hart, E. R.: J. Pharmacol. & Exper. Therap. 89:205, 1947. (5) Litter, M.; Ruiz Moreno, A., and Donin, L.: Ibid. 101:119, 1951. (6) Salamon, S. D.: Correspondence, J.A.M.A. 160:703 (Feb. 25) 1956. (7) Prien, E. L., and Walker, B. S.: J.A.M.A. 160:355 (Feb. 4) 1956. (8) Prien, E. L.: GP 15:80 (Feb.) 1957. (9) Mandel, H. G.; Redwell, V. W., and Smith, P. K.: J. Pharmacol. & Exper. Therap. 106:433, 1952. (10) Quick, A. J., and Ciesceri, L.: Ibid. 129:95, 1960. (11) Seeberg, V. P.; Hansen, D., and Whitney, B.: Ibid. 101:275, 1951.

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no calls at night for Mothe
(and no night calls **from**
Mother) thanks to Rynatan
Pediatric Formulations

just one
administration
at bedtime can relieve
children's respiratory
congestion and cough
for 10-12 hours

COLDS, sinusitis, rhinitis
Rynatan® suspension

decongests safely all day or all night with a single oral dose*

a good-lasting liquid nasal decongestant . . . in convenient dosage form for easier administration to infants and children

decongests air passages and dries secretions . . . with an effective oral vasoconstrictor combined with 2 superior antihistamines

virtually complete freedom from side effects . . . particularly drowsiness

proven safe and dependable . . . more published clinical reports than any other oral decongestant

Each 5 cc. contains:

Phenylephrine tannate, 5.0 mg.; Chlorpheniramine tannate, 2.0 mg.; Pyrilamine tannate, 12.5 mg.

Dosage:

Each 12 hours: Children 6 mos.-1 yr. ⅓ tsp.; 2-4 yrs. ½ tsp.; 5-7 yrs. 1 tsp.; 8-11 yrs. 2 tsp.; 12 yrs. and older 2-3 tsp. Adjust dosage as required.

RYNATAN is also available in tabule form for older children. *Each Rynatan tabule contains:* Phenylephrine tannate, 25 mg.; Chlorpheniramine tannate, 8 mg.; Pyrilamine tannate, 25 mg. *Dosage:* Each 12 hours: Children 6-7 yrs. ½ tabule; 8-11 yrs. ½ to 1 tabule; 12 yrs. and older 1-2 tabules.

COUGHS & congestion
New! Rynatuss™ suspension

inhibits the hyperactive cough reflex . . . decongests the entire breathing apparatus all day or all night with a single oral dose*

a new preparation . . . providing all the benefits of Rynatan suspension . . . plus cough control

suppresses nonproductive cough . . . with a dependable non-narcotic antitussive

decongests . . . with an effective oral vasoconstrictor plus a superior antihistamine

removes excessive secretions and assists expectoration . . . with a reliable and effective bronchodilator

safe for children . . . contains no opiate derivatives

Each 5 cc. contains:

Carbetapentane tannate (non-narcotic), 30 mg.; Ephedrine tannate, 5 mg.; Phenylephrine tannate, 5 mg.; Chlorpheniramine tannate, 4 mg.

Dosage:

Each 12 hours: Children 6 mos.-1 yr. ⅓ tsp.; 2-4 yrs. ½ tsp.; 5-7 yrs. 1 tsp.; 8-11 yrs. 2 tsp.; 12 yrs. and older 2-3 tsp. Adjust dosage as required.

RYNATUSS is also available in tabule form for older children. *Each Rynatuss tabule contains:* Carbetapentane tannate, 60 mg.; Chlorpheniramine tannate, 5 mg.; Ephedrine tannate, 10 mg.; Phenylephrine tannate, 10 mg. *Dosage:* Each 12 hours: Children 6-7 yrs. ½ tabule; 8-11 yrs. ½ to 1 tabule; 12 yrs. and older 1-2 tabules.

***Both Rynatan and Rynatuss Suspension employ Durabond®, the only long-acting principle proven by radioactive tracer studies to control drug blood levels in humans. (Bogner, R. L., and Moses, C.: Evaluation of a Sustained Release Principle in Human Subjects Utilizing Radioactive Technique, to be published, 1960.)**

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What more can I do?

Oatmeal breakfasts are naturally nutritious—help speed recovery after "flu" or colds

Quaker Oats and Mother's Oats are the same fine product.

When you recommend hot Oatmeal, mother will remember that it is a *naturally* nutritious food, rich in protein, thiamine and minerals. She knows it makes a breakfast the patient will enjoy. And she knows this is precious extra care which only mother can provide.

Each ounce of Quaker Oats provides 110 calories, 16.7% protein, 6.9% fat, 62.4% carbohydrates, and 1.5% roughage (crude fiber). Quaker Oats with milk contributes substantially to the dietary allowances recommended for thiamine, riboflavin, niacin and iron. Rich in phosphorus, low in sodium, Oatmeal has a high degree of dietary usefulness.

For additional information write: Medical Service Dept.

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9-Cup Coffee-Maker

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Doctor .....

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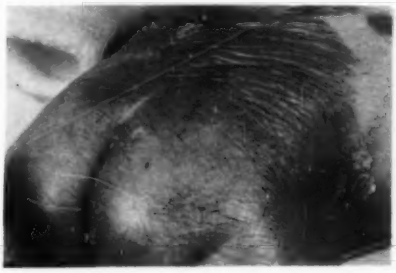
now...

healing and tissue-regenerating power for the severest case of diaper rash...

without resort to topical corticosteroids and antibiotics

methakote pediatric creme
(pat. appl. for)

A 3-month-old white male was hospitalized for severe diaper rash, which appeared quite pruritic. Treatment with 1% hydrocortisone cream for four weeks prior to admission had proved unsuccessful, diaper rash lesions becoming increasingly severe over this period.[1]



Five days later. METHAKOTE had been applied in thin layers on a b.i.d. schedule for five days. After the first 36 hours, improvement was quite noticeable. In addition to a lessening in erythema, the child appeared comfortable and cried less often.

Three weeks after admission. After five days of the b.i.d. treatment, METHAKOTE had been applied t.i.d. Improvement progressed to complete healing as shown. Nurses commented on the ease with which the cream could be washed from the patient's body and from their own hands.

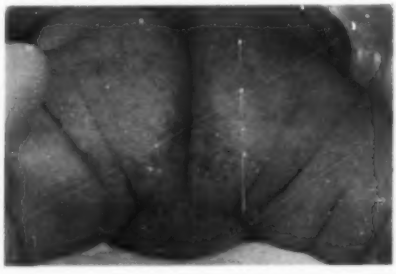
Treatment with METHAKOTE was continued at home; follow-up at weekly intervals revealed that new skin had formed nicely in the diaper area. At no time during prolonged use of METHAKOTE was there any side effect or idiosyncrasy-type reaction.

a new development from Borden's Pharmaceutical Division

whether the case is mild, moderate, or severe...clear diaper rash fast...and help keep it clear with **methakote** pediatric creme

Four-month-old male with diaper rash of one week's duration. Condition developed as a result of diarrhea contracted during epidemic on ship.[1]

Eleven days later. METHAKOTE treatment had been started on a t.i.d. schedule. One week later, after improvement had occurred, frequency of administration was reduced to b.i.d. Four days later healing was complete.



METHAKOTE* promotes rapid healing and tissue regeneration through a protein hydrolysate fortified with the amino acids, methionine and cysteine... shown to be especially important at the site of wound healing.[2-4]

Response is maintained and recurrences prevented by the antiseptic, benzethonium chloride, which eliminates *Bacillus ammoniagenes,* a causative factor in diaper rash.[5] This potent but nonirritating quaternary ammonium germicide also has been shown to inhibit the growth *in vitro* of *Staphylococcus aureus,* an organism often responsible for secondary pyogenic infection of the diaper area.

METHAKOTE establishes normal skin acidity and an optimal physiologic environment through the buffering action of the protein hydrolysate. Soothing and lubricating action is provided through Borden's washable, virtually nonsensitizing emollient vehicle, Dermabase.*

NONSTAINING GREASELESS WASHABLE

Available in 1½ oz. tubes and 3 oz. economy-size tubes.

1. Susca, L. A.: Treatment of diaper rash, New York J. Med., to be published. 2. Levine, A. J., et al.: Influence of amino acid therapy in chronic idiopathic pruritus ani, Gastroenterology 35:409, 1958. 3. Review: Requirements for sulfur amino acids, Nutrition Rev. 17:74, 1959. 4. Christian, J. R., and Gonzalez, F. A.: The topical treatment of acute and chronic diaper rash with an amino acid cream, Clin. Med., to be published. 5. Editorial: Diaper rash, J.A.M.A. 165:254, 1957.

*TRADE-MARK OF THE BORDEN COMPANY

Borden's

Pharmaceutical Division, 350 Madison Avenue, New York 17, N. Y.

PRINTED IN U. S. A.

In the school-age child..

when learning lags behind intelligence *and* behavior problems disturb the family

Deaner®-100

Tablets containing 100 mg. deanol as the acetamidobenzoate

The most frequently reported observations are improvement in social adaptation and scholastic performance, lengthening of attention span, and decrease in overactivity and irritability.

Deanol is a normal component of the brain of man.

Deaner-100 is virtually free from side-actions. It is not an MAO inhibitor. The only contraindication is grand mal epilepsy and mixed epilepsy with grand mal component.

Literature and file card on request

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FOR SIMULTANEOUS IMMUNIZATION AGAINST 4 DISEASES:

Poliomyelitis-Diphtheria-Pertussis-Tetanus

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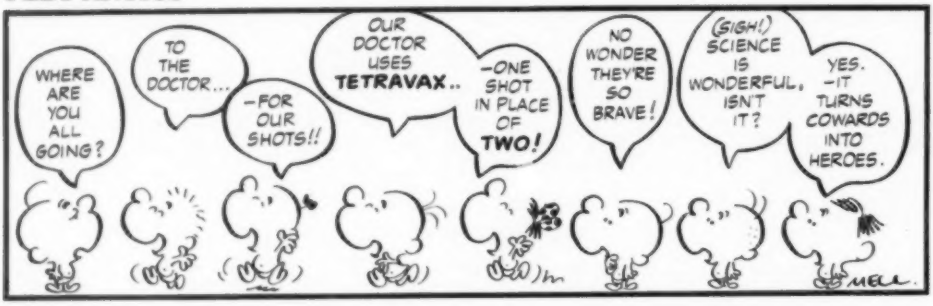
WHERE ARE YOU ALL GOING?
TO THE DOCTOR...
-FOR OUR SHOTS!!
OUR DOCTOR USES TETRAVAX..
-ONE SHOT IN PLACE OF TWO!
NO WONDER THEY'RE SO BRAVE!
(SIGH!) SCIENCE IS WONDERFUL, ISN'T IT?
YES. -IT TURNS COWARDS INTO HEROES.

TETRAVAX®

DIPHTHERIA AND TETANUS TOXOIDS WITH PERTUSSIS AND POLIOMYELITIS VACCINES

now you can immunize against more *diseases... with* fewer *injections*

Dose: 1 cc.
Supplied: 9 cc. vials in *clear plastic* cartons. Package circular and material in vial can be examined without damaging carton. Expiration date is on vial for checking even if carton is discarded.

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TETRAVAX IS A TRADEMARK OF MERCK & CO., INC.

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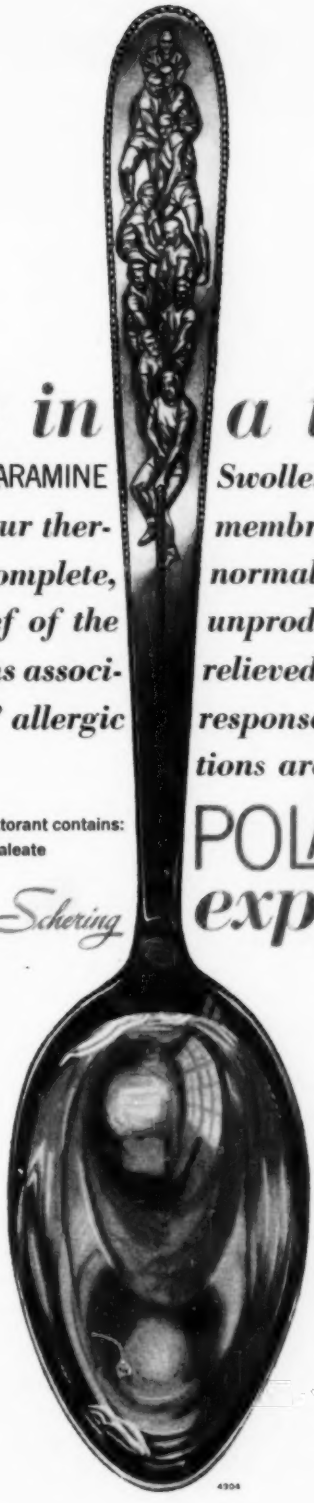
teamwork in a teaspoon



Each teaspoonful of POLARAMINE ***Expectorant provides four therapeutic effects for more complete, rapid and effective relief of the coughs and complications associated with your patients' allergic respiratory disorders.***

Swollen, congested mucous membranes are returned to normal rapidly, gently; dry, unproductive coughing is relieved; and further allergic response and its manifestations are reduced.

Each 5 cc. teaspoonful of POLARAMINE Expectorant contains:
2 mg. POLARAMINE (dexchlorpheniramine) Maleate
20 mg. d-Isoephedrine Sulfate
100 mg. Glyceryl Guaiacolate
Supply: 16 oz. bottles.

Schering

POLARAMINE®
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happy mother, cheerful baby

because their physician has kept
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with **DESITIN®**

OINTMENT

Protects against irritation of urine and excrement; markedly inhibits ammonia-producing bacteria; soothes, lubricates, stimulates healing.

For samples of Desitin Ointment, pioneer external cod liver oil therapy, write...

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DESIRABLE PROTEIN ALLOWANCE + PEDIATRIC CONTROL:

VARAMEL a formula that is completely flexible and offers a desirable protein allowance (4.2 gm/kg at 1:1 dilution plus carbohydrate) for healthy infants in normal *or* stress situations. You adjust the water and carbohydrate to meet the needs of the individual infant, confident that the protein in Varamel assures: ■ good growth, sound musculature ■ ample amounts of all milk nutrients ■ allowances to meet the stresses of respiratory ailments, fever, diarrhea ■ a water reserve for adequate renal function, proper water balance. The Baker Laboratories, Inc., Cleveland 3, Ohio

for those who prefer higher protein levels

"Personal experience with the hunger of infants fed even 3.5 Gm. (of protein) per kilogram makes us unwilling to recommend intakes of cow's milk which would give less protein. Although the determinants of food intake are complex, the possibility exists that unmet nutritional needs may make the intake of 3.5 Gm. and more of cow's milk protein necessary...."*

LACTUM (liquid and instant powder) supplies the higher protein level of modified milk formulas that has been used so successfully in the feeding of infants. In Lactum 16% of total calories is derived from protein.

*Gordon, H. H., and Ganzon, A. F.: J. Pediat. 54: 503 (April) 1959.

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modified milk formula

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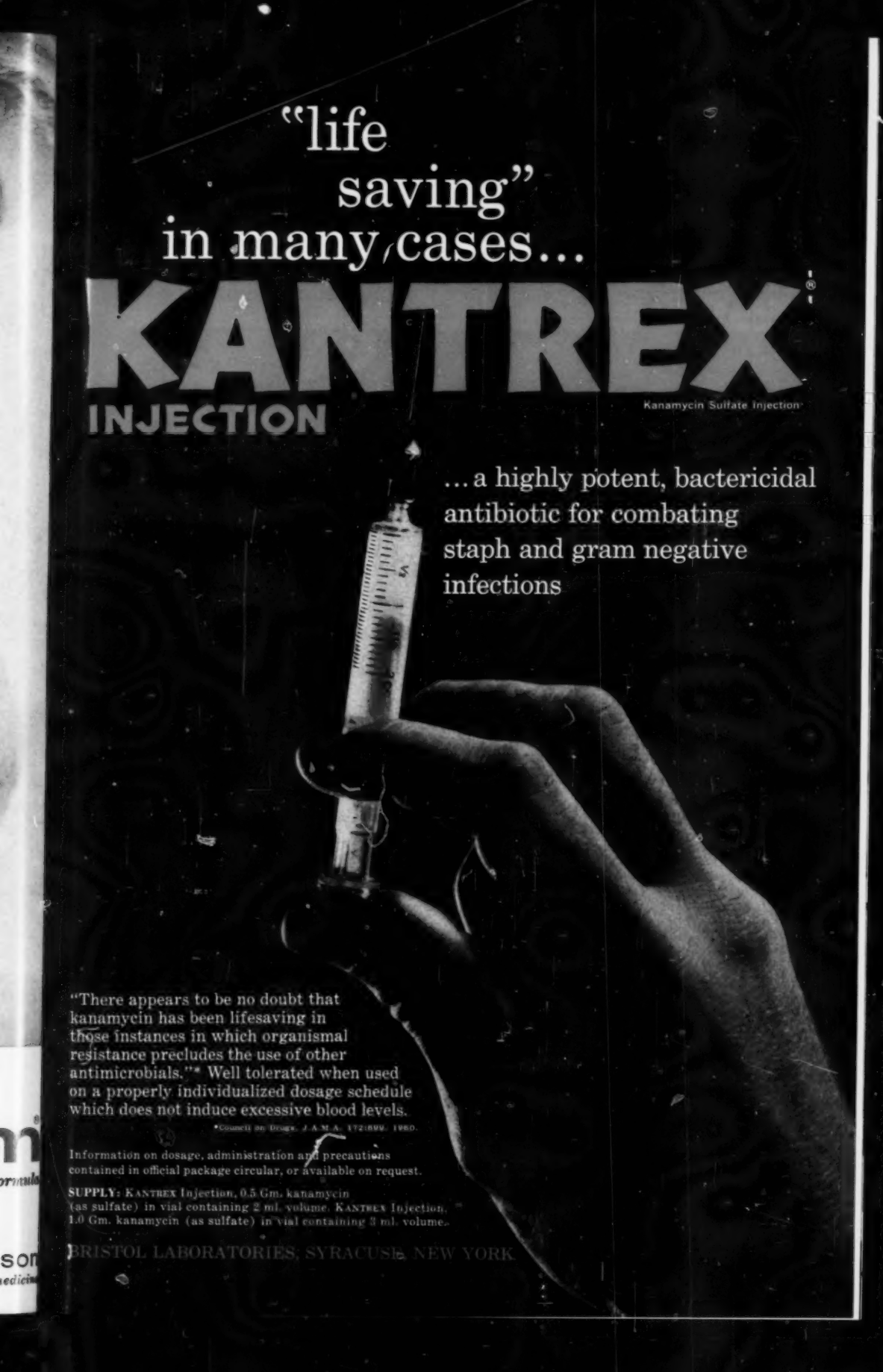
Symbol of service in medicine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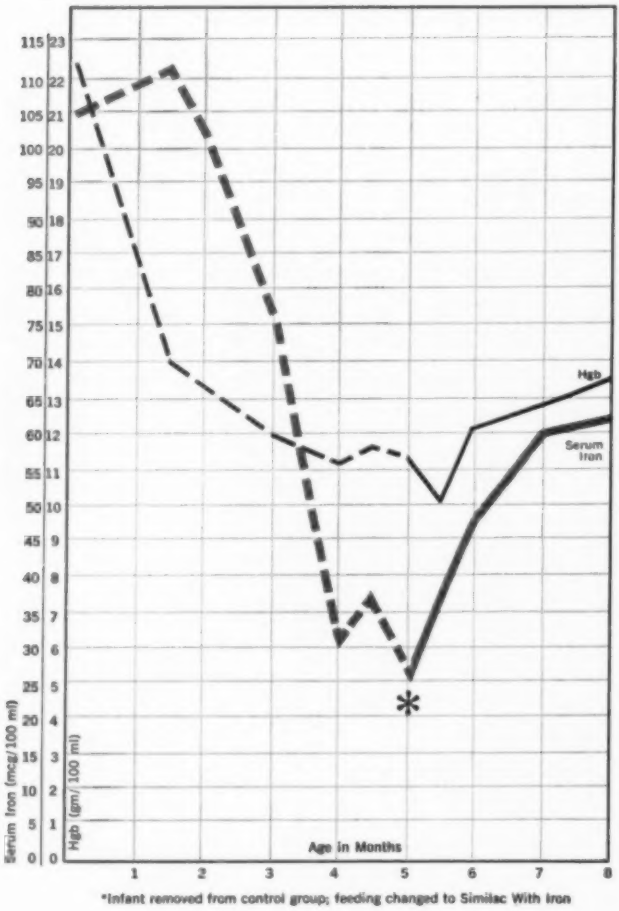
INJECTION
... a highly potent, bactericidal antibiotic for combating staph and gram negative infections
"There appears to be no doubt that kanamycin has been lifesaving in those instances in which organismal resistance precludes the use of other antimicrobials."* Well tolerated when used on a properly individualized dosage schedule which does not induce excessive blood levels.
*Council on Drugs. J.A.M.A. 172:899. 1960.
Information on dosage, administration and precautions contained in official package circular, or available on request.
SUPPLY: KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume. KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in vial containing 3 ml. volume.
BRISTOL LABORATORIES, SYRACUSE, NEW YORK

The hematologic progress of Infant #1810[1]



*Infant removed from control group; feeding changed to Similac With Iron

Male, healthy, one of a control group fed on evaporated milk formula

Decreased serum iron and elevated iron-binding capacity may precede by several weeks the fall in hemoglobin due to iron deficiency.[2] Prophylactic feedings of Similac With Iron (as with infant #1810[1]) can help prevent the development of clinical iron depletion.

Lahey points out, "Even a 'good' diet may, in the quantities eaten by an infant, provide less than the required amount of iron. . . evidence, then, suggests that though the physician should continue to recommend a 'good' diet, he should not depend solely on it for the prevention and cure of iron deficiency anemia in children."[2]

1. Marsh, A. K.: Personal communication.
2. Lahey, M. E.: Pediat. Clin. North America *4*:481 (May) 1957.

from a marginal deficiency to a comfortable margin with Similac With Iron®

12 mg of ferrous iron per quart of formula

Assured Iron Intake in every Feeding to { **maintain iron reserves** / **protect against iron deficiency states** / **support the usual diet**

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this is the Vi-Daylin moment. it comes once a day, and there is absolutely no mistaking how children feel about it. it belongs in a class with the cookie after dinner and the bedtime story. a treat become a habit. a good habit to prescribe. fun for the kids. peace for mom. assurance for you.

he most widely used and prescribed of all children's multivitamins VI-DAYLIN®

HOW DO YOU PREFER TO GIVE CHILDREN'S MULTIVITAMINS?

With a line like Vi-Daylin,® you can take care of your patient's daily needs, their changing needs—even their changing moods—clear up until their teens. And you'll know the kids are on your side. The famous Vi-Daylin flavor takes care of that.

Here are some of the ways you can give Vi-Daylin—

Most kids will love it—and lick it—right out of the spoon

The basic Vi-Daylin formula, of course, is a liquid, and comes in three bottle sizes—3 fl.oz., 8 fl.oz., and pints.

Then, for the holdouts—spring the "secret weapon" (mom will like it, too)

We're talking about the new pushbutton can, of course. For just a few cents more, mom can take home a 12 fl.oz. "Pressure Pak"—guaranteed to disarm little cynics and turn them into vitamin fans.

For young sophisticates—an honest-to-goodness lemon-candy tablet

And the nice thing is that it's *really* Vi-Daylin—same wonderful lemony flavor, same formula. One tasty Dulcet® tablet equals one teaspoon of liquid Vi-Daylin, and the tablets are so "grown-up."

When they need mineral supplement as well

ViDaylin-M provides all the essential vitamins *plus* eight valuable minerals. One teaspoon usually does the job—about ½ the dosage you would have had to recommend before ViDaylin-M came along.

And when a "therapeutic" dose is indicated

ViDaylin-T® is a high potency formula with the same lemony good taste as regular Vi-Daylin. Especially high in vitamins B_1 and C.

And remember: You can start the Vi-Daylin habit right in the first year

Vi-Daylin Drops, with eight essential vitamins in a delicious drops formula, have long been a standby in vitamin therapy from infancy through the first year. In 15-cc., 30-cc., and 50-cc. bottles with unbreakable calibrated dropper.

Pre-Daylin® Drops—for infants who need vitamins A, C, and D only. Tasty drops formula available in 15- and 50-cc. bottles with calibrated dropper.

VI-DAYLIN—Homogenized Mixture of Vitamins, A, D, B_1, B_2, B_6, B_{12}, C, and Nicotinamide, Abbott.
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The boy who wears his nose on his sleeve is more miserable than any adult in time of congestion.
He needs Biomydrin for prompt symptomatic relief. Biomydrin provides these multiple benefits: penetration of the mucous barrier; gentle decongestion, without irritation or rebound congestion; elimination of bacterial infection; control of allergic manifestations; and safety – Biomydrin is so safe that no special pediatric dosage form is required.
for pediatric nasal congestion
Biomydrin® nasal spray/drops
Formula: Mucus penetrating thonzonium bromide, 0.05%; antibiotic neomycin SO4, 0.1%, and gramicidin, 0.005%; decongestant phenylephrine HCl, 0.25%; antihistaminic thonzylamine HCl, 1.0%.
Indications: Common Colds/Sinusitis/Nasopharyngitis/Allergic Rhinitis/Hypertrophic Rhinitis
Dosage: Children over 3 – 1 or 2 sprays or 1 or 2 drops in each nostril, 4 or 5 times a day. Adults – 3 sprays or 3 drops in each nostril, 4 or 5 times a day.
Supplied: In convenient 15 ml. plastic atomizer, or 15 ml. bottle with dropper. Also available – Biomyurin® F Nasal Spray (Biomydrin with hydrocortisone alcohol 0.02%) – for more stubborn cases of edema and inflammation, particularly when associated with allergy.
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Vitamin-time is treat-time with tasty VIACETS Candispheres. Five delicious flavors — raspberry, cherry, orange, lemon and lime — in five pretty colors make VIACETS fun to take. Children *really* like them. And you will, too, for the complete pediatric vitamin support that VIACETS provide. Special layered construction assures potency, permits better chewing. Try VIACETS. Today.

delicious · chewable · multivitamin candispheres®

Each VIACETS Candisphere contains: Vitamin A...5,000 U.S.P. Units; Vitamin D...1,000 U.S.P. Units; Vitamin E...1.0 I.U. Units; ascorbic acid ...50 mg.; thiamine mononitrate...1.0 mg.; riboflavin...1.0 mg.; pyridoxine...1.0 mg.; calcium pantothenate...1.0 mg.; niacinamide...5.0 mg.; Vitamin B_{12}...2.0 mcg.; folic acid...0.1 mg. *Dosage:* One or two VIACETS daily, or as indicated. *Supplied:* Bottles of 120 multicolored candispheres.

WALKER LABORATORIES, INC., Mount Vernon, N. Y.

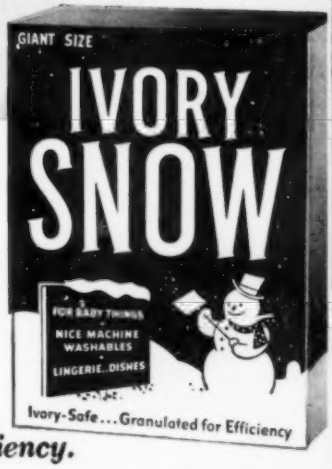
Viacets®

And for those patients needing just Vitamins A, D and C: delicious, orange-flavored, chewable ADCETS® Candispheres.

Why should you recommend Ivory Snow for baby's wash?

1. Because it's as safe a soap as a mother can use . . . leaves diapers and baby clothes soft, gentle-clean . . . and completely free from irritating deposits that can chafe tender skin!

2. Because it's as practical for mother as it is safe for baby— the only soap that gives a busy mother Ivory-safety in the efficient granulated form she needs for today's washing machines!

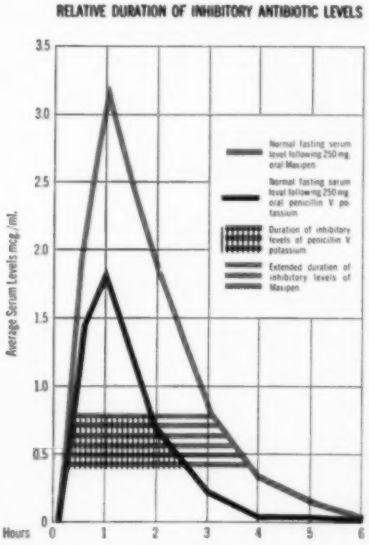


Only Ivory Snow is Ivory-safe and granulated for machine efficiency.

99 44/100% PURE® with Beauty Glow. A PROCTER & GAMBLE PRODU

an
orally maximal
penicillin

maximal serum concentration provides longer duration of inhibitory antibiotic levels for less susceptible organisms



The majority of penicillin-susceptible organisms are inhibited *in vitro* by very low concentrations of the antibiotic. Less frequently, susceptible organisms require somewhat higher concentrations. In the latter group, the period of MAXIPEN's inhibitory concentration is longer than that of penicillin-V, as can be seen in the chart at left. If the M.I.C. (minimum inhibitory concentration) for penicillin-V is slightly lower than for MAXIPEN, this may still hold true.

Although higher serum levels do not in themselves infer greater antibacterial activity, for those less susceptible organisms MAXIPEN may provide maximal exposure to inhibitory concentrations.

A TRIUMPH OF MAN OVER MOLECULE...
a product of Pfizer research

DOSAGE: *In moderately severe penicillin-susceptible infections,* 125 to 250 mg. three times daily. *In more severe conditions,* 500 mg. as often as every 4 hours around the clock.

MAXIPEN *may be administered without regard to meals.* However, highest absorption is achieved when it is taken just before or between meals.

NOTE: To date, allergic reactions have not been less with MAXIPEN than with older oral penicillins. Usual precautions regarding penicillin administration should be observed.

SUPPLIED: MAXIPEN TABLETS, scored, *125 mg.,* bottles of 36; *250 mg.,* bottles of 24 and 100. MAXIPEN FOR ORAL SOLUTION, each 5 cc. of reconstituted liquid containing *125 mg.,* available in 60 cc. bottles.

REFERENCES *on phenethicillin potassium (α-phenoxyethyl penicillin potassium):* 1. Gourevitch, A., *et al.,* Antibiotics Ann. 1959/60, pp. 111-118. 2. Pindell, M. H., *et al., Ibid.,* pp. 119-126. 3. Morigi, E. M. E., *et al., Ibid.,* pp. 127-132. 4. Cronk, G. A., *et al., Ibid.,* pp. 133-145. 5. Osment, Lamar S.: Pilot Study of Alpha-Phenoxyethyl Penicillin in Skin Infections, Clin. Med. 7:523 (Mar.) 1960. 6. Garrod, L. P.: Relative Antibacterial Activity of Three Penicillins, Brit. M. J. (Feb. 20) 1960, p. 527.

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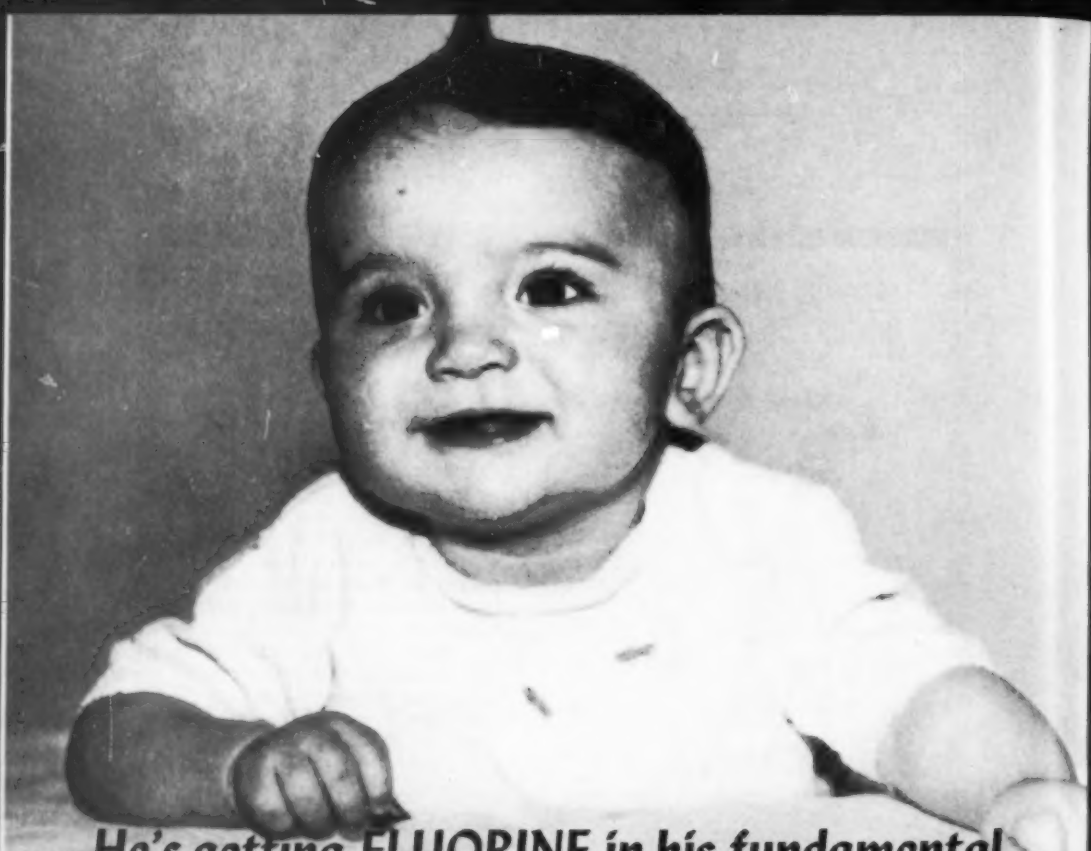

He's getting FLUORINE in his fundamental vitamin drops..... Funda-Vite(F)®

Andy's pediatrician has supplemented Andy's daily diet, since birth, with 0.6 ml. of FUNDA-VITE(F). Thereby, Andy has the advantage over many babies in that he is receiving good nutritional support *plus being safeguarded against future dental caries as well.*

Extensive evidence exists that fluoride supplementation should be started at birth . . . during the formative calcifications of teeth . . . and continued until age 10 for maximum dental benefits.[1-2] Inasmuch as dentists seldom see infants and young children, preventive methods in dental health should be included in pediatric care.[2]

Daily supplementation of 400 U.S.P. units of vitamin D and 30 mg. of vitamin C for normal healthy infants and children has been widely endorsed.[3-6] In combination with 0.5 mg. fluorine — a controlled vitamin-fluorine dosage is possible with a minimal effort on the part of the mother . . . affording the utmost in convenience and economy.

Each 0.6 ml. of FUNDA-VITE(F) contains 400 U.S.P. units vitamin D, 30 mg. vitamin C and 0.5 mg. fluorine (as sodium fluoride). AVAILABLE ON YOUR PRESCRIPTION ONLY in 30 ml. and 50 ml. bottles with calibrated dropper.

NEW! for children age 3 and over — FUNDA-VITE(F) LOZI-TABS™. Each tablet contains 400 U.S.P. units vitamin D, 30 mg. vitamin C and 1 mg. fluorine (as sodium fluoride). AVAILABLE ON YOUR PRESCRIPTION ONLY in bottles of 100 LOZI-TABS.

400 U.S.P. units vitamin D and 30 mg. of vitamin C per 0.6 ml. (without fluorine) is available as FUNDA-VITE® in 30 ml. bottles with calibrated dropper.

REFERENCES: 1.) Council on Dental Therapeutics: Prescribing Supplements of Dietary Fluorides. J. Am. Dental Assoc. 56:589 (April) 1958. 2.) Trieger, N.: Fluoride Administration: Role of the Pediatrician. Delivered at New England Pediatrics Society Meeting, Boston, March 16, 1960. 3.) Council on Foods and Nutrition: Vitamin Preparations as Dietary Supplements and as Therapeutic Agents. J.A.M.A. 169:110 (Jan. 3) 1959. 4.) May, C. D.: Editorial. Pediatrics 23:833 (May) 1959. 5.) Sebrell, Jr., W. H.: Vitamins in Medical Practice. Seminar Report. 3:2. (Fall) 1958. 6.) Smith, D. W., Blizzard, R. M. and Harrison, H. E.: Idiopathic Hypercalcemia. Pediatrics 24:268 (August) 1959).

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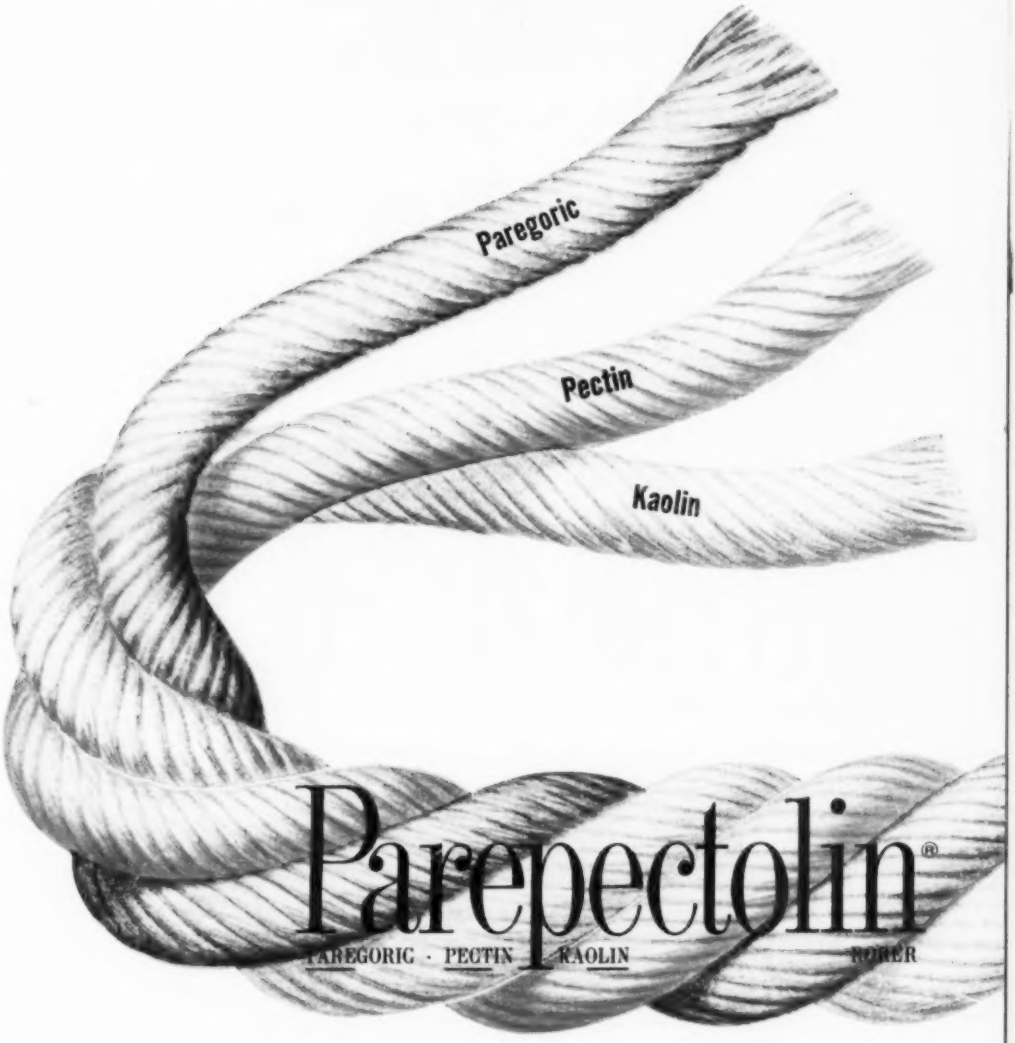
HOYT PHARMACEUTICAL CORP., Newton, Mass.

to **CONTROL DIARRHEA**...the traditional and time-tested triad of effective and safe agents



Pleasant taste *plus* predictable, prompt response in diarrhea

Parepectolin combines paregoric, pectin, kaolin in *a balanced, stable colloidal suspension*, with a smooth, creamy consistency and a pleasant, mildly aromatic flavor. Parepectolin is compatible with antibiotics, and retains its uniform consistency and its good flavor.

Parepectolin; each fluid ounce—Paregoric (equivalent) 1.0 dram, Pectin 2.5 gr., Kaolin (specially purified) 85 gr. Bottles of 4 and 8 fluid ounces.

ROHER WILLIAM H. RORER, INC. PHILADELPHIA, PENNSYLVANIA

a mustache is to wear on Halloween

dogs are to kiss people

a face is something to have on the front of your head

REDISOL® is so kids have better appetites

Redisol (Cyanocobalamin, crystalline vitamin B_{12}) often stimulates children's appetites with consequent weight gain. Tiny **Redisol Tablets** (25, 50, 100, 250 mcg.) dissolve instantly in the mouth, on food or in liquids. Also available: cherry-flavored **Redisol Elixir** (5 mcg. per 5-cc. teaspoonful); **Redisol Injectable,** cyanocobalamin injection USP (30 and 100 mcg. per cc., 10-cc. vials and 1000 mcg. per cc. in 1, 5 and 10-cc. vials).

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ANNOUNCING—
SPECIFICALLY FOR
INFECTIONS DUE TO
"RESISTANT" STAPHYLOCOCCI

AN ENTIRELY NEW SYNTHETIC
"STAPH-CIDAL" PENICILLIN

Staphcillin™

sodium dimethoxyphenyl penicillin
FOR INJECTION

UNIQUE—BECAUSE IT
RETAINS ANTIBACTERIAL
ACTIVITY IN THE PRESENCE OF
STAPHYLOCOCCAL PENICILLINASE
WHICH INACTIVATES
OTHER PENICILLINS

Bristol™

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STAPHCILLIN™

(sodium dimethoxyphenyl penicillin)

For Injection

DESCRIPTION

STAPHCILLIN is a unique new synthetic parenteral penicillin produced by Bristol Laboratories for the specific treatment of staphylococcal infections due to resistant organisms. Its uniqueness resides in its property of resisting inactivation by staphylococcal penicillinase. It is active against strains of staphylococci which are resistant to other penicillins.

Each dry filled vial contains: 1 Gm. STAPHCILLIN (sodium dimethoxyphenyl penicillin), equivalent to 900 mg. dimethoxyphenyl penicillin activity.

INDICATIONS

STAPHCILLIN is recommended as specific therapy only in infections due to strains of staphylococci resistant to other penicillins, e.g.:

Skin and soft tissue infections: cellulitis, wound infections, carbuncles, pyoderma, furunculosis, lymphangitis and lymphadenitis.

Respiratory infections: staphylococcal lobar or bronchopneumonia, and lung abscesses combined with indicated surgical treatment.

Other infections: staphylococcal septicemia, bacteremia, acute or subacute endocarditis, acute osteomyelitis and enterocolitis.

Infections due to penicillin-sensitive staphylococci, streptococci, pneumococci and gonococci should be treated with Syncillin® or parenteral penicillin G rather than STAPHCILLIN. Treponemal infections should be treated with parenteral penicillin G.

DOSAGE AND ADMINISTRATION

STAPHCILLIN is well tolerated when given by deep intragluteal or intravenous injection.

As is the case with other antibiotics, the duration of therapy should be determined by the clinical and bacteriological response of the patient. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic and cultures are negative. The usual duration has been 5-7 days.

Intramuscular route: The usual adult dose is 1 Gm. every 4 or 6 hours. Infants' and children's dosage is 25 mg. per Kg. (approximately 12 mg. per pound) every 6 hours.

Intravenous route: 1 Gm. every 6 hours using 50 ml. of sterile saline solution at the rate of 10 ml. per minute.

* *Warning:* Solutions of STAPHCILLIN and kanamycin should not be mixed, as they rapidly inactivate each other. Data on the results of mixing STAPHCILLIN with other antibiotics are being accumulated.

DIRECTIONS FOR RECONSTITUTION

Add 1.5 ml. sterile distilled water or normal saline to a 1 Gm. vial and shake vigorously. Withdraw the clear, reconstituted solution (2.0 ml.) into a syringe and inject. The reconstituted solution contains 500 mg. of STAPHCILLIN per ml. Reconstituted solutions are stable for 24 hours under refrigeration.

For intravenous use, dilute the reconstituted dose in 50 ml. of sterile saline and inject at the rate of 10 ml. per minute.

*This statement supersedes that in the Official Package Circulars dated September and/or October, 1960.

(Continued)

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MICROBIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

In vitro studies show that STAPHCILLIN is a bactericidal penicillin with activity against staphylococci resistant to penicillin G. Strains of staphylococci so far tested have been sensitive to STAPHCILLIN *in vitro* at concentrations of 1-6 mcg. per ml. These levels are readily attained in the blood and tissues by administration of STAPHCILLIN at the recommended dosage. This unique attribute is probably due to the fact that STAPHCILLIN is stable in the presence of staphylococcal penicillinase. STAPHCILLIN also resists degradation by *B. cereus* penicillinase. The antimicrobial spectrum of STAPHCILLIN with regard to other microorganisms is qualitatively similar to that of penicillin G; but considerably higher concentrations of STAPHCILLIN are required for bactericidal activity than is the case with penicillin G.

STAPHCILLIN is rapidly absorbed after intramuscular injection. Peak blood levels (6-10 mcg./ml. on the average after a 1.0 Gm. dose) are attained within 1 hour; and then progressively decline to less than 1 mcg. over a 4 to 6 hour period. It is poorly absorbed from the gastrointestinal tract. STAPHCILLIN is rapidly excreted by the kidney.

As shown by animal studies, STAPHCILLIN is readily distributed in body tissues after intramuscular injection. Of the tissues studied, highest concentrations are reached in the kidney, liver, heart and lung in that order; the spleen and muscles show lower concentrations of the antibiotic. STAPHCILLIN diffuses into human pleural and prostatic fluids, but its diffusion into the spinal fluid has not yet been completely studied. However, one patient with meningitis showed a significant concentration in his spinal fluid while on STAPHCILLIN therapy.

Toxicity studies with STAPHCILLIN and penicillin G in animals show that they have approximately the same low order of toxicity.

Certain staphylococci can be made resistant to STAPHCILLIN in the laboratory, but this resistance is not related to their penicillinase production. During the clinical trials, no STAPHCILLIN-resistant strains of staphylococci were observed or developed; the possibility of the emergence of such strains in the clinical setting awaits further observation.

PRECAUTIONS

During the clinical trials, several mild skin reactions, e.g., itching, papular eruption and erythema were observed both during and after discontinuance of STAPHCILLIN therapy. Patients with histories of hay fever, asthma, urticaria and previous sensitivity to penicillin are more likely to react adversely to the penicillins. It is important that the possibility of penicillin anaphylaxis be kept in mind. Epinephrine and the usual adjuvants (antihistamines, corticosteroids) should be available for emergency treatment. Because of the resistance of STAPHCILLIN to destruction by penicillinase, parenteral *B. cereus* penicillinase may not be effective for the treatment of allergic reactions. Information with regard to cross-allergenicity between penicillin G, penicillin V, phenethicillin (Syncillin) and STAPHCILLIN is not available at present. If superinfection due to Gram-negative organisms or fungi occurs during STAPHCILLIN therapy, appropriate measures should be taken.

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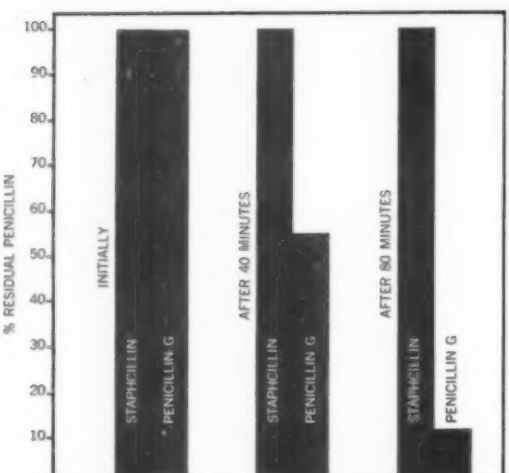

In the presence of staphylococcal penicillinase, STAPHCILLIN remained active and retained its antibacterial action. By contrast, penicillin G was rapidly destroyed in the same period of time.
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PROFESSIONAL INFORMATION SERVICE—The attached Official Package Circular provides complete information on the indications, dosage, and precautions for the use of STAPHCILLIN. If you desire additional information concerning clinical experiences with STAPHCILLIN, the Medical Department of Bristol Laboratories is at your service. You may direct your inquiries via collect telephone call to New York, PLaza 7-7061, or by mail to Medical Department, Bristol Laboratories, 630 Fifth Ave., N. Y. 20, N. Y.

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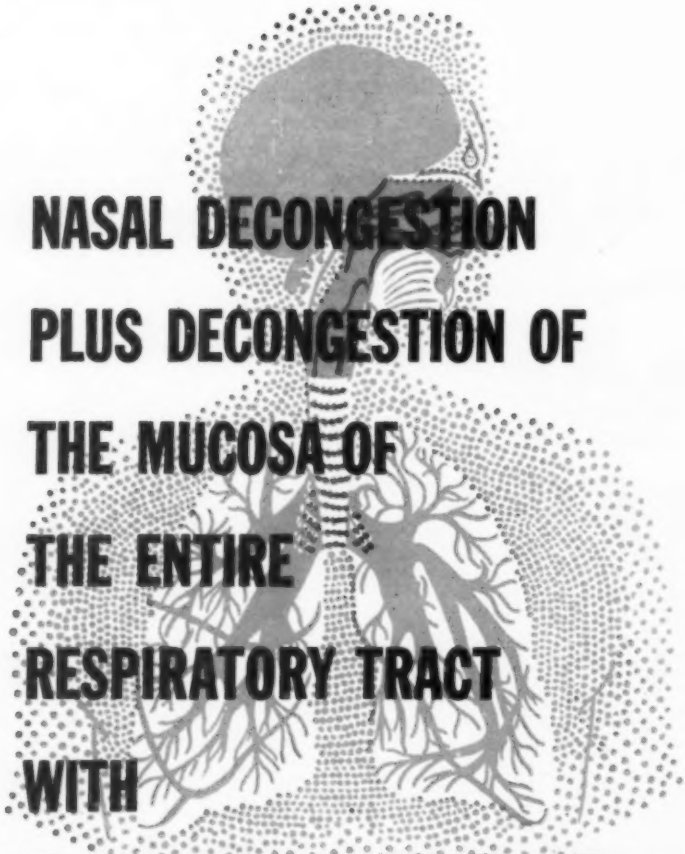

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1. Research Laboratories, Mead Johnson & Company, unpublished data, available on request. 2. Holt, L. E., Jr., and McIntosh, R.: Holt Pediatrics, ed. 12, New York, Appleton-Century Crofts, Inc., 1953, p. 224.

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1. Stephens, V. C., *et al.*: J. Am. Pharm. A. (Scient. Ed.), *48*:620, 1959.
2. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, *1*:320 (May), 1960.
3. Kuder, H. V.: Clin. Pharmacol. & Therap., in press.

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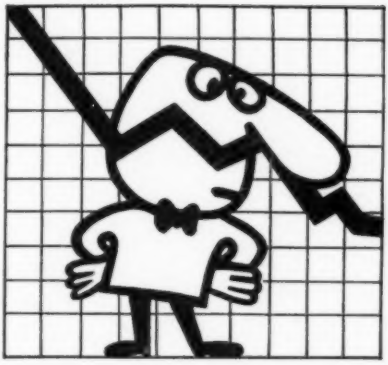

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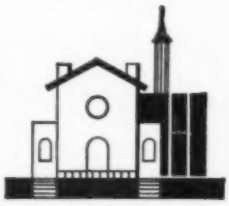

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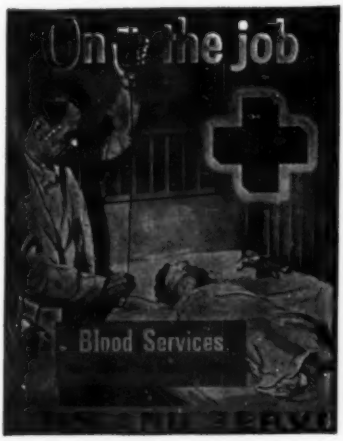

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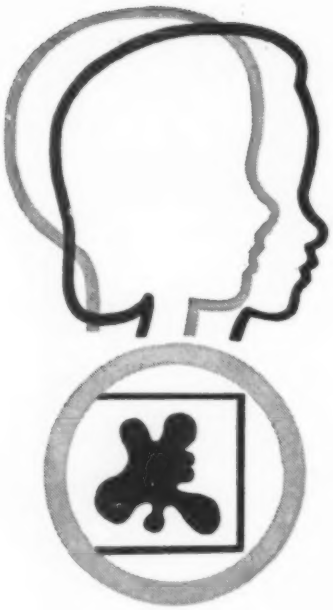

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Glyceryl Guaiacolate	100 mg.

Dosage: Adults and children over 12 years—2 tsp., 4 times daily. Children 6 to 12 years—1 tsp., 4 times daily. Infants and children up to 6 years—½ tsp., 4 times daily.

Precaution: Although pseudoephedrine hydrochloride causes virtually no pressor effect in normotensive patients, it should be used with caution in patients with hypertension. In addition, even though triprolidine hydrochloride produces only a low incidence of drowsiness, appropriate precautions should be observed.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

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2. Committee on Nutrition: Pediat. 21:860 (May) 1958.
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